Rare Diseases of the Immune System
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Periodic and Non-Periodic Fevers

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Foreword

Periodic diseases have long held a special fascination for physicians and scientists alike. In ancient times, such illnesses were tied to natural phenomena, such as the phases of the moon. Later, it became clear that the periodicity of some illnesses, such as malaria, is linked to the life cycle of the causative organism, while in other cases, such as relapsing fever, periodicity is the result of the "cat and mouse" game between a microbial pathogen and the host immune response. More recently, with the discovery of *CLOCK* genes, some forms of biologic periodicity could be explained by molecular pathways with an intrinsic oscillation constant.

Our understanding of the periodic fever syndromes evolved within this conceptual landscape. By the 1980s, it was well-established that the periodicity of some febrile illnesses, such as those noted above, is driven by host-pathogen interactions. Yet there remained an intriguing group of illnesses, the best recognized of which was familial Mediterranean fever (FMF), in which there was recurrent fever without any overt evidence of infection. The ethnic predilection of FMF, taken together with its autosomal recessive inheritance, strongly suggested a disease mechanism intrinsic to the host. With the advent of the Human Genome Project and positional cloning, I was drawn to FMF as an "experiment of nature" through which we could discover a molecular tuning fork regulating fever and inflammation in humankind.

Ultimately, we were successful in discovering the *MEFV* gene and its encoded protein, pyrin. Although not immediately obvious at the time, pyrin and its eponymous N-terminal fragment have helped to define multiple innate immune molecules and pathways, in some cases leading to life-altering targeted therapies. Moreover, the positional cloning of *MEFV* was the first in a long progression of gene discoveries defining new monogenic febrile disorders and a new family of illnesses—the autoinflammatory diseases—that are inborn errors of the innate immune system. This concept has been subsequently extended to genetically complex illnesses, such as systemic-onset juvenile idiopathic arthritis, Still's disease, Behçet's disease, and the syndrome of periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA). In most cases, both the monogenic and genetically complex disorders are more aptly described as *recurrent* rather than *periodic,* and the cyclicity and responsiveness to environmental cues vary greatly even among family members harboring the same genetic variant. Many of these disorders are elegantly described in this volume.

Notwithstanding the significant advances in the field of autoinflammation, there are still many puzzles awaiting the enquiring mind. Perhaps most notable, we still do not have a clear concept of the periodicity (or episodic nature) of these illnesses. For disorders like PFAPA, in which the attacks are predictable months in advance, it seems likely that there may be a feedback loop between the host microbiome and the developing lymphoid tissue of the oropharynx, but the details remain elusive. Even for disorders like FMF, which are admittedly more recurrent than periodic, we are far from a molecular account of how attacks are triggered and how they are ultimately turned off.

This dialectic of mystery and discovery is exactly how it should be in science. I truly hope that you will find this volume to be your own travel guide to this exciting new world of human disease and your inspiration to take the field to the next level.

February 6, 2019

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Preface

Recurrent fevers are a frequent problem in children. While infections are the most common causes, genetic and autoinflammatory disorders have been increasingly recognized. These syndromes are sometimes very difficult to diagnose, and several can be discovered only after a thorough work-up for fever of unknown origin, but improvements in genetic techniques have allowed more and more precise definitions. Enormous advancements have been achieved in treatment with the use of biologic therapies, in particular with the cytokine inhibitors.

This volume includes the description of several classic conditions as well as of novel and rarer forms. The authors of these chapters are international experts in the field and have provided clear descriptions of the clinical findings and of therapeutic implications. The readers, whether general pediatricians, pediatric rheumatologist, or immunologist, will certainly benefit from these updated informations, which we tried to keep as practical as possible.

Milan, Italy — Rolando Cimaz

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Periodic and Non-Periodic Fevers

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Marco Gattorno

1.1 Cryopyrin-Associated Periodic Syndromes (CAPS)

CAPS are a group of clinical conditions identified in different times and secondary to autosomal dominant mutations of a single gene, NLRP3 (NOD-like receptor 3), encoding a protein called cryopyrin [1]. FCAS, also named familial cold urticaria, familial polymorphous cold eruption, and cold hypersensitivity, was first described in 1940 as a rare autosomal dominant disorder characterised by intermittent episodes of rash, fever, and arthralgia secondary to exposure to cold [2]. MWS was first described in 1962 in a British family with recurrent episodes of urticaria-like eruptions, fever, chills, malaise, and limb pain since childhood associated with progressive development of sensorineural hearing loss and amyloidosis [3]. In 1981, Prieur and Griscelli described three unrelated children presenting since birth with a syndrome characterised by a permanent skin rash, fever, lymphadenopathy, severe central nervous system involvement (mental retardation, sensorial hearing loss, and chronic aseptic meningitis), chronic arthropathy, peculiar facial and dysmorphic features [4]. They defined this syndrome as CINCA syndrome (MIM 607115), whereas American authors defined the same entity as neonatal onset multisystemic inflammatory disease (NOMID).

1.1.1 Pathogenesis

Interleukin-1β (IL-1β) plays a pivotal role in the pathogenesis of many inflammatory conditions and represents a potential target of therapeutic intervention in many inflammatory diseases. The increasing knowledge of the pathogenic consequences

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related to mutations of genes involved in the monogenic autoinflammatory diseases has shed light on some pivotal pathophysiological mechanisms related to the activation and secretion of IL-1β [5].

IL-1β lacks a secretory signal peptide and is externalised by monocytic cells through a non-classical pathway, arranged in two steps and involving a multiprotein intracellular complex, called inflammasome, responsible for activation of the IL-1 converting enzyme (or caspase-1), which in turn converts pro-IL-1β to the mature, active 17 kDa form.

The stimulation of cells of the innate immunity with an external PAMP (pathogens associated molecular pattern), such as lipopolysaccharide (LPS) toward the Toll-like receptor 4 (TLR4), induces the gene expression and the synthesis of the inactive IL-1β precursor (pro-IL-1β) (Fig. 1.1) [6]. Monocytes stimulated with LPS alone release approximately only 20% of the IL-1β over 24–48 h. After priming, the NLRP3-Inflammasome activation requires a second signal, usually the extracellular ATP that determines an intracellular depletion of potassium after its binding to its specific cellular purinergic receptor P2x7R. A wide range of exogenous (whole pathogens, PAMPS, toxins) and endogenous (products of cell death, indicators of metabolic stress, crystals, mitochondrial reactive oxygen species, ROS) stimuli can activate the NLRP3 inflammasome (Fig. 1.1).

Mutations of NLRP3 in humans are associated with a gain of function that leads to an excessive and faster production of IL-1β after stimulation of TLR, even in the

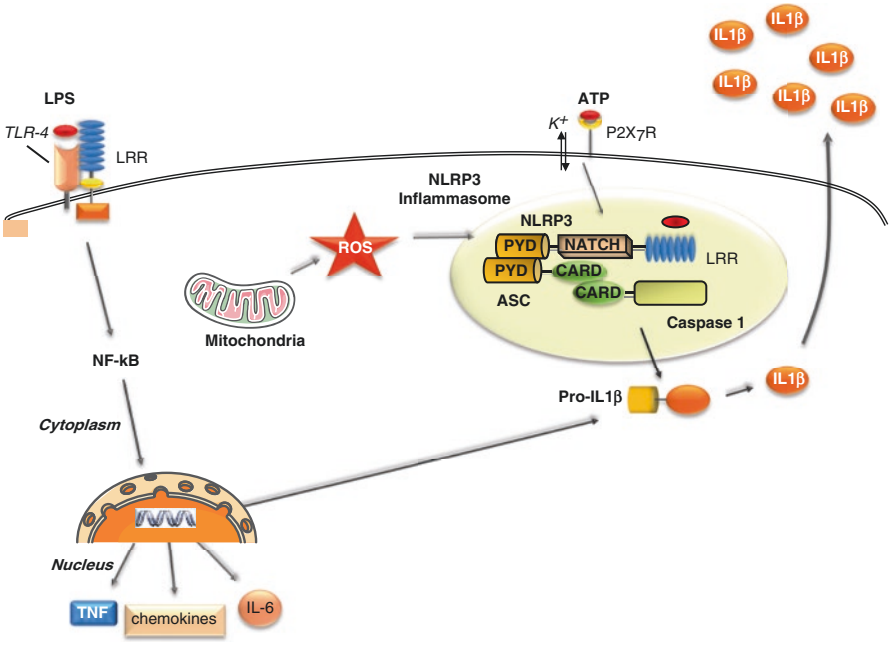

Fig. 1.1 Activation of the NLRP3 Inflammasome. *LPS* lipopolysaccharide, *ROS* reactive oxygen species, *TLR* toll-like receptor, *LRR* leucine rich repeat, *IL-1* interleuchin-1

absence of a second signal, like ATP. This is caused by a state of overactivation of the redox state observed in NLRP3-mutated monocytes from CAPS patients that cause a faster production and secretion of IL-1β after TLRs' stimulation [7, 8].

1.1.2 Clinical Picture and Diagnostic Approach

FCAS is characterised by urticarial rash and fever spikes of short duration (usually <24 h) induced by generalized cold exposition [2]. Arthralgia and conjunctivitis are also common. Other symptoms seen after cold exposure include profuse sweating, drowsiness, headache, extreme thirst, and nausea. MWS is characterised by recurrent episodes of urticaria and fever that may develop in early infancy. The fever episodes (usually <38.5 °C) can be associated with the same clinical manifestations as seen in FCAS (arthralgia, conjunctivitis, drowsiness) but usually are not strictly evoked by cold exposure. Acute phase reactants are raised during fever episodes and may persist at a slightly increased level also during fever-free intervals. During the course of the disease, neurosensorial deafness and polyarthritis may develop. Amyloid A (AA) amyloidosis is a complication of the late stage of the disease [9]. CINCA represents the more severe phenotype associated with NLRP3 mutations. It presents with a chronic and inflammatory disease course that differentiates this condition from the classical periodic fevers. The urticaria-like rash may develop during the first weeks of life. Patients present a typical "facies" characterised by frontal bossing, saddle back nose, and mid-face hypoplasia. Bony overgrowth predominantly affecting the knees (including the patella) is the most characteristic feature of this form. A chronic inflammatory polyarthritis may be also present, sometime leading to bone erosions. Central nervous system manifestations include chronic aseptic meningitis that can lead to cerebral atrophy, ventriculomegaly and to a severe mental retardation. Increased intracranial pressure, sensorineural hearing loss and chronic papilledema, with associated optic nerve atrophy, and loss of vision are also typical findings in untreated patients. Patients display a persistent elevation of acute phase reactants, leucocytosis and chronic anaemia [10, 11]. Recently, novel diagnostic criteria for all CAPS phenotypes have been developed by a group of experts and validated with a number of confounding diseases [12]. Evidence-based classification criteria have been also developed on the basis of the comparison of different monogenic and multifactorial conditions collected enrollled in the Eurofever registry [13].

So far, more than 200 different variants have been reported in the NLRP£ gene (http://fmf.igh.cnrs.fr/infevers/). Of course not all of them are associated with a phenotype consistent with a cryopyrinopathy. Almost all the observed pathogenic mutations are found in the exon 3 of the NLRP3 gene, coding for the NACHT domain of the cryopyrin that plays a crucial role in the oligomerisation of the protein. Different mutations are associated with a milder or more severe alteration of the structure of the protein and therefore are associated to a milder or more severe phenotype [11]. Recently, a genotype-phenotype analysis has been developed in the context of all CAPS patients included in a large international registry, Eurofever

[14]. Notably, there are other NLRP3 variants (such as V198M and Q703K), that are considered low-penetrance mutations (V198M) or even common polymorphisms (Q703K), being detected also in a percentage of healthy carriers. These variants should be considered with a great caution in the diagnostic work-up patients with an inflammatory phenotype [15].

Germline mutations of the NLRP3 gene are found in almost 70% of patients with a CAPS phenotype. Notably, a relevant percentage of CAPS patients negative for germline mutations are carriers of somatic mosaicisms that should be systematically searched for in patients with a typical phenotype with a negative genetic standard test [16, 17].

1.1.3 Treatment

The crucial role of NLRP3 in the control of caspase 1 activation and the massive secretion of active IL-1β seen in cryopyrin-mutated subjects suggested that anti-IL1 treatment might be an effective treatment. Indeed, the recombinant IL-1 receptor antagonist, anakinra, has a dramatic effect on the control of rash and constitutional symptoms in patients with the all subtypes of CAPS [9, 18–22]. It is today established that IL-1 inhibitors are the treatment of choice in CAPS patients. The goal of the treatment is a complete control of the inflammatory symptoms and the normalization of the acute phase reactants. Anakinra has been approved by the FDA and in Europe for the treatment of CAPS. Canakinumab is a fully human anti-interleukin-1β monoclonal antibody that selectively blocks IL-1β. Canakinumab is used subcutaneously at the dose of 150 mg (or 2 mg/kg) every 8 weeks. In patients with the more severe CINCA phenotype, higher doses (4 mg/kg) and frequency of administration are often required [23]. Canakinumab is approved for the use in all subtypes of CAPS in patients older than 2 years. A third IL-1 blocker (rilonacept) is available in the United States but is not licensed in Europe.

1.2 Familial Mediterranean Fever (FMF)

FMF is the most common among hereditary recurrent inflammatory disorders [24]. This disease affects populations of Mediterranean descent: Arabs from the East and from the West, Armenians, Turks, non-Ashkenazi and other Jews, but also Italians, Greeks. Among non-Ashkenazi Jews and Turks, the frequency of heterozygotes in the general population is greater than 1/5.

In 1997, the gene associated with FMF was cloned by two international consortia [25, 26]. It was called MEFV for MEditerranean FeVer. The gene encodes a protein called marenostin/pyrin consisting of 781 amino acids. MEFV is a gene expressed specifically in myeloid cells.

Pyrin has several domains: the pyrin domain is a specific domain of 90 amino acids located in the N-terminal region. The second domain called B30.2 or SPRY is

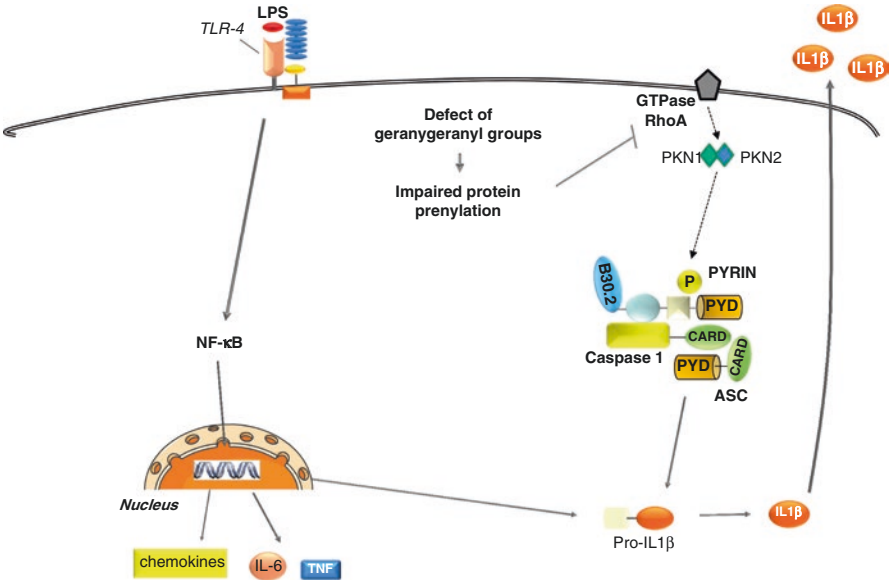

Fig. 1.2 The pyrin inflammasome. RhoA activates the serine-threonine kinases PKN1 and PKN2 that phosphorylate pyrin. Phosphorylated pyrin binds to regulatory proteins that in turn block the pyrin inflammasome. This regulatory mechanism is greatly altered with mutant pyrin: the binding to regulatory proteins of mutant pyrin is substantially decreased, with a constitutive IL-1β release from peripheral blood mononuclear cells of patients with FMF. In MDK, the shortage of the geranylgeranyl groups induces a defect of prenylation that leads to RhoA inactivation and consequent pyrin inflammasome activation

located in the C-terminal region of the protein and contains the most frequent mutations associated with FMF.

The functional role of pyrin remained largely unknown for many years after its identification. Preliminary studies suggested its possible regulatory role on the NLRP3 inflammasome [27, 28]. Pyrin is indeed able to interact with some crucial elements of the NLRP3 inflammasome, such as ASC and caspase 1, and it was postulated that pyrin mutations could induce a loss-of function in its potential inhibitory action on the NLRP3 Inflammasome (Fig. 1.2).

Recently, an alternative hypothesis has been proposed: pyrin forms, with ASC and caspase 1, its own "pyrin inflammasome" [29, 30], able to activate IL-1 in response to bacterial modifications of the GTPase RhoA [31]. RhoA activates the serine-threonine kinases PKN1 and PKN2 that phosphorylate pyrin. Phosphorylated pyrin binds to regulatory proteins that in turn block the pyrin inflammasome. This regulatory mechanism is greatly altered with mutant pyrin: the binding to regulatory proteins of mutant pyrin is substantially decreased, with a constitutive IL-1β release from peripheral blood mononuclear cells of patients with FMF [9]. According to this model pyrin variants would represent gain-of-function mutations enhancing the activity of the "pyrin inflammasome" [30, 31] (Fig. 1.2).

1.2.1 Clinical Picture and Diagnostic Approach

FMF has a disease onset before 5 years of age in two-thirds of patients. Fever is typically associated with signs of acute serosal inflammation: peritonitis (95%), pleuritis (45%,), scrotitis (3%) and pericarditis (1%). Large joints are also affected in more than 50% of patients—mainly knees, hips and ankles. Erysipelas-like erythema of the lower limbs is the most typical skin lesion, even if uncommon. Attacks last for about 24–72 h and resolve spontaneously. Their recurrences have no regular periodicity. Some factors can trigger inflammatory attacks in FMF, especially physical or emotional stress, menstruation, and travel. Except for amyloidosis, chronic manifestations of the disease such as encapsulating peritonitis and chronic destructive arthritis affecting especially hips and knees are rare. At least in children, the severity of the clinical manifestations is related not only to genetic factors (i.e., severe variants affecting exon 10) but also to environmental factors, such as country of residence [32].

Despite advances in genetic testing the diagnosis of FMF still relies on clinical grounds [33]. Three different sets of diagnostic criteria have been developed mainly in populations in which FMF has a high prevalence (Table 1.1) [34–36].

The performances of the three Hashomer, Livneh Tel-Hashomer, and Yalcinkaya FMF criteria were assessed in pediatric patients with FMF compared to other periodic fevers, including MKD, TRAPS, CAPS, PFAPA, and undefined periodic fever of different ethnicity enrolled in the large international Eurofever registry. Patients with FMF were correctly diagnosed using the pediatric Yalcinkaya criteria with a sensitivity rate of 87.4%, but with a low specificity (40.7%). On the other hand, Tel Hashomer and Livneh criteria displayed a sensitivity of 45.0% and 77.3%, respectively, but a better specificity, 97.2% and 41.1% for the Tel Hashomer and Livneh criteria, respectively [37]. In 2015, Federici et al. developed and validated a new set of clinical criteria for the classification of patients affected by the four main autoinflammatory recurrent fever syndromes, including FMF (Table 1.2) [13].

In a clinical context, the presence of two mutations on different alleles (homozygosity or compound heterozygosity) confirms the diagnosis. When only one mutation is present, the diagnosis is not ascertained but should not be ruled out if the clinical presentation is typical: although five mutations represent more than 85% of all the mutations, some rare or unknown mutations exist (http://fmf.igh.cnrs.fr/infevers/) [38]. It is also likely that some heterozygous patients may have attenuated clinical signs. According to this theory, in cohorts of patients with periodic fever syndrome it has been observed that the frequency of typical FMF symptoms decreases from patients carrying two high penetrance mutations towards patients with a single one low-penetrance mutation [39]. Clinical signs may appear in heterozygotes probably due to the presence of yet unknown modifying factors such as additional molecular defect(s) and/or particular environmental factors [32, 40]. Large series show that patients with one single mutated allele may present a clinical picture of FMF. However, heterozygosity in the MEFV gene constitutes only a susceptibility factor for the disease that need to be combined to the presence of still unknown genetic or environmental factors to explain the clinical picture [32, 39–41].

Table 1.1 Criteria for the diagnosis of familial Mediterranean fever[a]

Criteria of Livneh
Major criteria
Typical attacks
1. Peritonitis (generalised)
2. Pleuritis (unilateral) or pericarditis
3. Monoarthritis (hip, knee, ankle)
Minor criteria
1–3. Incomplete attacks involving one or more of the following sites:
1. Abdomen
2. Chest
3. Joint
4. Exertional leg pain
5. Favourable response to colchicine
Supportive criteria
1. Family history of familial Mediterranean fever
2. Appropriate ethnic origin
3. Age < 20 years at disease onset
4–7. Features of attacks: 4. Severe, requiring bed rest, 5. Spontaneous remission, 6. Symptom-free interval
7. Transient inflammatory response, with one or more abnormal test result(s) for white blood cell count, erythrocyte sedimentation rate, serum amyloid A and/or fibrinogen
8. Episodic proteinuria/haematuria
9. Unproductive laparotomy or removal of 'white' appendix
10. Consanguinity of parents

[a]The requirements for diagnosis of familial Mediterranean fever are ≥1 major criterion, or ≥2 minor criteria, or 1 minor plus ≥5 supportive criteria, or 1 minor criterion plus ≥4 of the first 5 supportive criteria. Typical attacks are defined as recurrent (≥3 of the same type), febrile (rectal temperature of ≥38 °C) and short (lasting between 12 h and 3 days). Incomplete attacks are defined as painful and recurrent attacks that differ from typical attacks in one or two features, as follows: (1) the temperature is normal or < 38 °C; (2) the attacks are longer or shorter than specified (but no shorter than 6 h or longer than a week; (3) no signs of peritonitis are recorded during the abdominal attacks; (4) the abdominal attacks are localised; (5) the arthritis is in joints other than those specified. Attacks are not counted if they do not fit the definition of either typical or incomplete attacks

Amyloid nephropathy was the most severe long-term complication and the more frequent cause of death in FMF before the colchicine era. FMF-associated amyloidosis is a prototype of the inflammatory amyloidosis or AA amyloidosis, which complicates longstanding inflammatory diseases. Amyloidosis generally occurs in patients with early and severe inflammatory attacks (FMF phenotype 1) [42]. The risk of developing AA amyloidosis is closely linked to the duration and intensity of the inflammatory state as reflected by the level of serum AA (SAA). SAA and C-reactive protein (CRP) are both increased during FMF attacks, as well as in all forms of hereditary fevers. However, amyloidosis may occur exceptionally in patients with no recognised clinical inflammatory crisis (Phenotype 2) [43]. Phenotype 2 is probably exceptional, as shown in a Turkish study in which proteinuria was measured in relatives of patients with FMF amyloidosis [19]. It has long

Table 1.2 The preliminary Eurofever classification criteria

FMF (cut-off > 65)	
PRESENCE	score
Duration of episodes <2 days	7
Chestpain	11
Abdominal pain	9
South Mediterrean ethnicity	20
North Mediterranean ethnicity	8
ABSENCE	score
Aphtous stomatitis	10
Exudative pharyngitis	7
Urticarial rash	13
Enlarged cervical lymphonodes	8
Duration of episodes >6 days	15

CAPS (cut off >61)	
PRESENCE	score
Arthralgia	17
Urticarial rash	34
ABSENCE	score
Abdominal pain	26
Exudative pharyngitis	23

MKD (cut off > 41)	
PRESENCE	score
Painful lymphnodes	13
Aphtous stomatitis	11
Generalized enlargment of lymphonodes OR splenomegaly	8
Age at onset <2 years	10
Diarrhea (sometimes/often)	20
Diarrhea (always)	37
ABSENCE	score
Chestpain	11

TRAPS (cut off 44)	
PRESENCE	score
Periorbital oedema	27
Duration of episodes >6 days	22
Myalgia	12
Relatives affected	8
Age at disease onset>3	3
ABSENCE	score
Vomiting	11
Aphtous stomatitis	16

been established that the prevalence of amyloidosis varies according to ethnic groups. This suggests that genetic and/or environmental factors participate in the occurrence of amyloidosis during FMF. Several correlation studies have shown a preferential association between amyloidosis and the M694V mutation in the homozygous state. The occurrence of amyloidosis is influenced by modifier genes, among which are genes encoding SAA—namely, SAA1 and SAA2, and several polymorphic variants [44].

In patients with FMF, the homozygous SAA1.1 genotype is associated with an increased risk of amyloidosis, compared with other genotypes at the SAA1.1 locus. This was first observed in Armenian patients and has been confirmed in patients with FMF from other populations. Whereas the major role of the SAA1 locus in the risk of developing amyloidosis has been clearly identified in many studies, including patients with other underlying diseases such as rheumatoid arthritis, and other populations such as Japanese patients, the precise mechanism underlying this observation is still to be elucidated.

1.2.2 Treatment

Daily colchicine is an effective treatment for preventing recurrence of attacks and the occurrence of amyloidosis [45]. The usual dose of colchicine is 1 mg/day [46]. If the disease activity is not controlled, either because of recurrence of attacks or because of persistently raised inflammatory parameters, especially SAA, the dose of

colchicine should be increased by 0.5 mg/day every 3–6 months up to 2.5 mg/day [47]. Diarrhea due to colchicine is rare and can be managed by splitting the dose in two during the day. In some cases, proteinuria due to amyloidosis disappears during treatment with colchicine.

Although colchicine intoxication remains a serious concern, long-term daily colchicine is relatively safe. Adverse effects of colchicine on sperm function are controversial but now considered as not being deleterious; long-term use of colchicine can be considered as safe, including during pregnancy [46].

True non-responders to colchicine are rare; most of them are non-compliant patients. In these non-responders, interferon-α has been proposed, but promising early results have not been confirmed. More recently, IL-1 blockers (anakinra, rilonacept, and canakinumab) have shown efficacy in some patients who were resistant to colchicine, in agreement with the pathogenic data obtained on marenostin/pyrin role in the IL-1 secretion pathway [48]. Monoclonal antibody against IL-1beta (canakinumab) was effective in small series of FMF patients resistent to colchicne [49, 50]. Recently, a placebo-controlled randomized clinical trial has clearly shown the efficacy of this drug in colchicine resistent FMF [51]. Canakinumab is now approved for this indication by FDA and EMA.

1.3 Mevalonate Kinase Deficiency (MKD)

MKD was originally identified in 1984 in six patients of Dutch ancestry with a long history of recurrent attacks of fever of unknown cause and a high serum IgD level [52]. For this reason, this disorder has also been named hyper IgD syndrome or Dutch fever.

High IgD plasma levels have been used as a diagnostic hallmark until mutations in the mevalonate kinase (MVK) gene, encoded on chromosome 12q24, were identified as the cause of the disease [53, 54]. The complete deficiency of this enzyme causes a distinct syndrome called mevalonic aciduria (MA; MIM 251170), which is clinically characterised by severe mental retardation, ataxia, failure to thrive, myopathy and cataracts; notably, these patients also have recurrent fever attacks [55]. MVK is an essential enzyme in the isoprenoid biosynthesis pathway, which producess several biomolecules involved in different cellular processes (Fig. 1.2).

The distribution of MKD is not limited to northern European populations. Indeed, a relevant number of patients have been observed also among populations living around the Mediterranean basin and Asia. Moreover, owing to the low sensitivity and specificity of IgD serum levels, the term hyper IgD syndrome has been replaced by mevalonate kinase deficiency associated periodic syndrome.

1.3.1 Pathogenesis

The pathogenetic mechanisms that link the dysregulation of mevalonate pathway to the inflammatory phenotype are only partially understood. MVK catalyses the

ATP-dependent phosphorylation of mevalonate to 5-phosphomevalonate and is the first enzyme to follow the highly regulated enzyme hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase in isoprenoid biosynthesis. Cells from patients with the MKD phenotype still contain residual MVK enzyme activities (from 1% to 8% of the activities of control cells), while in cells from patients with the MA phenotype the MVK enzyme activity is below the detection level (approximately 0.1% that of normal individuals). This enzymatic deficiency is also reflected in the high levels of mevalonic acid in plasma and urine in patients with MA and low to moderate levels of mevalonate acid in patients with periodic fever associated with MKD.

In vitro studies have shown that shortage of isoprenoid end products (mainly the geranylgeranyl groups), rather than an excess of mevalonate, contributes to the inflammation in MKD [56]. It has recently been demonstrated that the shortage of the geranylgeranyl groups induces a defect of prenylation that leads to RhoA inactivation and consequent pyrin inflammasome activation (Fig. 1.2) [31]. These data demonstrate a previously unsuspected fundamental molecular connection between FMF and MKD.

1.3.2 Clinical Picture and Diagnostic Approach

Disease onset occurs very early in life, most often the first 2 years; almost all patients have developed the disease during the first decade of life [57]. Fever attacks have an abrupt onset and last 4–6 days. Irritability and general poor conditions during the attacks are quite common. Severe abdominal pain often accompanied by vomiting and/or diarrhea is frequently associated with fever attacks. Cervical lymphadenopathy is common; axillary, inguinal, and intra-abdominal lymph node enlargement may be also present. Splenomegaly is seen during fever attacks in about half of patients. Erythematous macules and urticaria-like lesions are frequent cutaneous manifestations. Oral aphthous lesions might be also observed. Articular involvement occurs in the majority of patients as arthralgia or as an oligoarticular, usually symmetric, arthritis [57]. Usually patients carrying milder mutations (see below) present a complete wellbeing between fever attacks, with a normal growth. In a subgroup of patients the more severe impairment of the enzymatic activity secondary to MVK mutations with a deleterious effect, lead to a sub-chronic inflammatory phenotype associated to persistent elevation of acute phase reactants, hepatosplenomegaly, chronic arthritis, failure to thrive and a slightly impaired cognitive development, the so-called intermediate phenotype. This latter phenotype is clearly a continuum between MKD with periodic fever and mevalonic aciduria.

In MKD patients with periodic fever, the symptoms persist for years, but usually tend to become less prominent with time. However, in some patients the disease may progress towards adulthood. Amyloidosis was not considered as a possible long-term complication of MKD, but it has been recently described in rare patients.

Neutrophilia and raised acute phase reactants are present during fever attacks. Increased plasma levels of IgD (>100 IU/ml) during episodes of fever and in basal conditions have been considered in the past as a hallmark of the disease. However,

the specificity of this finding is low. Concomitant elevation of IgA has been also reported. An increased urine excretion of mevalonic acid is seen during fever spikes and decreased MVK activity may also point towards the diagnosis. However, the above mentioned determinations need a highly specialised laboratory and therefore are often difficult to perform as a screening test. Thus the decision to undergo molecular analysis of the MVK gene in a child with periodic fever is usually taken on clinical grounds.

Since MKD has the higher clinical overlap with the more frequent and multifactorial PFAPA syndrome, a diagnostic score has been developed in order to identify those children with recurrent fever at higher risk to carry mutations of MVK, MEFV and TNFRSF1A genes [58]. The score has been validated in Western european populations only and is available at www.printo.it/diagnosticscore. Evidence-based classification criteria for MKD have been recently developed on the basis of the comparison of different monogenic and multifactorial recurrent fevers enrolled in the Eurofever registry [13].

MKD is an autosomal recessive disease. So far more than 215 substitutions or deletions of the MVK gene have been reported (http://fmf.igh.cnrs.fr/infevers/) [38]. Some variants (i.e., V310M, A334T) are strongly associated with a severe MA phenotype and with a severely impaired cellular MVK activity. The most common mutation in the MVK gene is the V377I variant, which is associated with the mild phenotype of MKD and with a residual MVK activity. It is found in the compound heterozygous state in the vast majority of patients with the periodic fever associated with MKD [57]. Other mutations such as H20P and I268T have also been associated either with MA and MKD phenotype (http://fmf.igh.cnrs.fr/infevers/) and might be associated to the intermediate phenotype [14]. More recently other hereditary diseases has been linked to the MKD gene: disseminated superficial actinic porokeratosis (DSAP) [48, 59] and very rare inherited retinal diseases [60] are due to mutations in the MKD gene, showing further that mutations of a single gene can manifest with very different phenotypes. Even if up to date, no ocular involvement has been described in MKD-associated periodic syndrome patients; this finding highlights that all the patients should undergo a regular ocular assessment.

1.3.3 Treatment

Fever attacks usually respond dramatically to the administration of steroids (prednisone: 1 mg/kg/day as single administration or, in more severe attacks, with a short course of 3–5 days) [48]. However, owing to the high frequency of the fever episodes, some patients may need almost continuous treatment [61].

The use of biological treatments is largely anecdotal and sometimes controversial. Anti-TNF therapy has been found to reduce the frequency and intensity of fever attacks in some patients, but not in others. The use of IL-1 blockers has been described as effective in some anecdotal cases, even if the percentage of patients with a complete response to Anakinra in the Eurofever registry was lower than

reported for other monogenic diseases [57]. In an open-label study, MKD patients showed an excellent response to the use of IL-1 monoclonal antibody (canakinumab) [62]. Recently a placebo-controlled randomized clinical trial has clearly shown the efficacy of this drug in MKD, TRAPS, and colchicine-resistant FMF [51]. In this study, MKD patients needed higher doses of the drug and a more frequent administration (4 mg/kg every 4 weeks) when compared to the other two conditions. Canakinumab is now approved for MKD by FDA and EMA.

1.4 TNF-Receptor-Associated Autoinflammatory Syndrome (TRAPS)

TRAPS is due to dominant mutations of the p55kd TNF receptor superfamily type 1A (TNFRSF1A) [63]. Even though TRAPS was initially described in subjects of Nordic origin, as emphasised by the name familial Hibernian fever, mutations in TNFRSF1A have now been found in many populations, including Black Americans, Japanese and those of Mediterranean ancestry [64, 65].

1.4.1 Pathogenesis

Early studies of TRAPS suggested that inflammation was mediated by a defect in the shedding of the soluble extracellular domain of TNFR1. This defect could impair the shedding of the membrane bound receptor and decrease the circulating levels of soluble TNFR1. Soluble TNF receptors (p55 and p75 kD, type 1B) play a crucial role in the down-modulation of the pro-inflammatory effect of TNF, binding the cytokine in the circulation and preventing the activation of membrane-bound receptors. However, normal plasma concentration of the soluble form of the receptor during attacks have been found and, even more importantly, treatment with a fusion protein of the soluble part of the p75 receptor (etanercept) produce only a modest and transient response in most TRAPS patients (see below) reflecting the fact that the mechanisms that drive the inflammation in TRAPS mutations do not rely on a quantitative or qualitative abnormality of the soluble form of the receptor. Subsequent studies have shown that most TRAPS-associated TNFR1 mutants are clearly accumulated and retained in the endoplasmic reticulum (ER), which suggests that the mutations most likely affect protein folding and trafficking to the membrane [66, 67]. Some studies suggest that the mutated TNFR1 receptor might retain some functionality and that it can still signal at the ER and promote ER-stress induced activation of proinflammatory MAP kinases [68]. Furthermore, cells carrying TNSRFS1A mutations try to override the accumulation of mutant unfolded proteins through an intracellular mechanism called Autophagy. The exhaustion of this process may lead to the activation of the NLRP3 inflammasome and is therefore responsible for the increased secretion of IL-1β observed in TRAPS patients [69] (Fig. 1.3). This latter mechanism explains the apparent paradox of the better response to anti-IL-1 than anti-TNF agents in TRAPS patients.

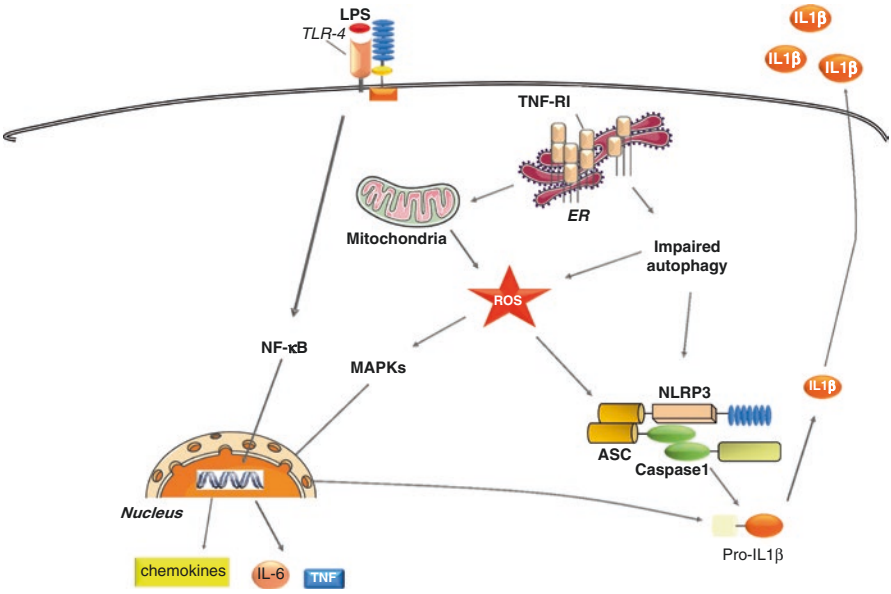

Fig. 1.3 Effect of unfolded protein response and endoplasmatic reticulum (ER) stress in the pathogenesis of TRAPS

1.4.2 Clinical Picture and Diagnostic Approach

TRAPS attacks last longer than in FMF and MKD, generally more than 5 days and up to 3 weeks, even though attacks shorter than 5 days have been reported [70]. Abdominal pain can simulate a surgical event, like for FMF. Skin manifestations are present in more than three quarters of cases. A wide spectrum of rashes can be seen: urticaria-like, plaques and patches. The most distinctive lesion is represented by erythematous, swollen, warm, and tender plaques of various sizes with hazy edges, usually affecting the upper and lower limbs but also the chest. Usually, the rash has a migratory course from the root to the extremity of the limbs. This pseudocellulitis is often accompanied by painful myalgias and constitutes the other most distinctive manifestation of TRAPS attacks. Myalgias are frequently observed and might herald the onset of the attacks. Although magnetic resonance imaging shows an abnormal signal in subcutaneous tissue, fasciae and muscles during TRAPS attacks, biopsies reveal that only fasciae were infiltrated by lymphocytes and monocytes, without myositis. Thoracic, scrotal pain, arthritis, orbital oedema and conjunctivitis are also found in TRAPS attacks. Renal amyloidosis is the main complication of TRAPS syndrome, being present in the majority of untreated patients. Increased levels of serum amyloid A not only during the fever attacks but also in the symptoms-free intervals detect patients with an increased risk of developing this complication.

TRAPS is an autosomal recessive disease. The careful examination of the family tree might help the identification of other affected members. As for FMF, some TRAPS patients display a subclinical disease course with persistent elevation of acute phase reactants and SAA. If not properly recognized these patients may develop AA amyloidosis, that represented the more frequent and severe complication in pre-biologic treatment era. A relative who died for renal insufficiency due to amyloidoses was a common finding in the family history of many TRAPS patients.

At present, 158 variants of the TNFRSF1A gene have been reported (http://fmf.igh.cnrs.fr/infevers/) [38]. Most TRAPS-associated mutations, including a majority of cysteine substitutions, are located in the first two cysteine-rich domains of the TNFRSF1A protein and are likely responsible of the proposed pathogenesis. The meaning of two variants, R92Q and P46L has not been completely determined [71]. P46L appears rather as a benign polymorphism and R92Q behaves at most as an incomplete penetrance mutation with no accumulation of the receptor in the ER.

At least in Caucasian populations, the R92Q mutation is the most frequently observed variant of the TNFRSF1A gene. According to different studies, the allele frequency of the R92Q variant in the general population ranges from 1.2% to 4%. As stated above, R92Q is a missense and low-penetrance mutation with no relevant impact on the structure and function of the mutated protein and is usually associated with a milder disease course, characterised by episodes of fever lasting only a few days, lower intensity of disease-associated symptoms and much lower prevalence of amyloidosis [72]. The majority of children with periodic fever and the R92Q mutation display a milder disease course than patients with structural mutations and a higher rate of spontaneous resolution and amelioration [73]. These clinical observation supports the limited pathogenic role of this variant. Based on these data and on the prevalence of this variant in the normal population, great caution should be taken in the interpretation of a positive molecular analysis for the R92Q variant, especially in children with periodic fever.

1.4.3 Treatment

Corticosteroids can attenuate the length and the severity of an attack when given at its onset [48]. In the most severe forms of the disease, clinical signs of inflammation are almost permanent and require daily use of corticosteroids, leading to dependency and requiring the use of other anti-inflammatory drugs [61]. Colchicine does not seem to prevent recurrences of TRAPS attacks. Some benefit has been described in patients carrying the R92Q variant. Theoretically, TNF inhibitors seem designed to be an optimal treatment of TRAPS. Nevertheless studies describing the use of etanercept report, despite the overall beneficial effects both on clinical manifestations and laboratory parameters, a discontinuation of the treatment in most of the treated patients due to lack of complete efficacy [74]. Furthermore, a paradoxical reaction with exacerbation of the inflammatory signs has been seen after administration of the anti-TNF monoclonal antibody (infliximab) in some patients with TRAPS and thus this type of drugs should not be used in this indication [48].

Recently published data suggested an excellent response to IL1 inhibitors in some patients. Anakinra was firstly used in one adult patient for few months [75] and subsequently in 5 TRAPS patients (4 children and 1 adult) for a longer follow-up, with good response [76]. Data from the Eurofever registry confirm the better performance of IL-1 blockade compare with anti-TNF treatment in TRAPS patients [48]. These observations lead to the recommendation of using IL1 inhibitors as a first-line treatment if corticosteroids failed to control symptoms [61]. In an open-label study involving 20 patients with severe disease course, canakinumab (IL-1 monoclonal antibody) showed a complete control of disease activity in 90% of the patients [77]. Recently a placebo-controlled randomized clinical trial has clearly shown the efficacy of canakinumab in TRAPS [51]. Canakinumab is now approved for TRAPS by FDA and EMA.

1.5 Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome (PFAPA)

Within this acronym are classified those children presenting with periodic fever attacks similar to those seen in monogenic periodic fevers but negative for mutations of known genes (MEFV, MVK, TNFRS1A). Although some anecdotic familial cases of PFAPA have been reported, it does not have a documented genetic basis. No specific ethnic background for PFAPA has been also demonstrated.

PFAPA was first described by Marshall et al. in 1987 [78]. The disease usually develops before 5 years of age. It is characterised by fever spikes of abrupt onset lasting 3–6 days; fever recurs regularly every 2–6 weeks, although an explanation for its clockwork periodicity is lacking.

The fever flare-ups are usually heralded by chills. Children with PFAPA syndrome often appear to be in good condition even during the fever spikes; this is a clinical feature that may help to distinguish PFAPA from the other form of periodic fevers associated with a genetic defect. Nevertheless some older children complain of general malaise and myalgia. The aphthous lesions seen in PFAPA are small and localised to labial gingival tissues and are rapidly self-remitting. Cervical lymph node enlargement is common (and may be relevant); enlarged lymph nodes are tender and normalise with the resolution of the fever attack. Acute phase reactants and neutrophils are elevated during attacks and completely normalise during the periods of complete wellbeing. The disease has a benign course and tends to remit spontaneously [79].

Recently, a comparison of the clinical manifestations seen in 518 patients with genetically-confirmed inherited periodic fevers (291 FMF, 74 MKD, 86 TRAPS, 67 CAPS) and 199 PFAPA patients was analyzed in the Eurofever registry [13]. The clinical features included in the classical PFAPA triad (pharyngitis, enlargement of cervical lymph nodes and apthous stomatitis) were by far the most common manifestations. However, the same features were also observed in other inherited diseases, mainly in MKD. Conversely, other clinical features reported in different PFAPA series (such as abdominal pain, arthralgia, myalgia, vomiting, diarrhea) were clearly less prevalent when compared to inherited periodic fevers.

The diagnosis of PFAPA is based on clinical diagnostic criteria: the modified Marshall criteria that remain highly nonspecific [80]. Indeed these criteria display also a low specificity, as almost 50% of genetically positive children (especially MKD) also fulfil the PFAPA criteria, which therefore do not represent a specific tool for selecting patients with high probability of being negative at genetic testing [81]. Some clinical manifestations during fever attacks, such as abdominal and chest pain and gastrointestinal symptoms (vomiting and/or diarrhea), should be considered as indicating a higher risk of carrying mutations of known genes. The diagnosis of PFAPA is generally based on a number of variables (dramatic onset of attacks, lack of response to antibiotics, repetitive presence of cardinal symptoms and prompt response to steroids) that are much more complex than the mere satisfaction of the current diagnostic criteria.

Patients are treated with oral steroids on the first day of the crisis with success. However, their administration could decrease the interval between attacks. Case series and prospective studies showed good responses to tonsillectomy; but all these studies lack a long follow-up period and most are non-controlled.

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Fever of Unknown Origin

2

Estíbaliz Iglesias, Antoni Noguera-Julian, Laia Alsina, and Jordi Antón

2.1 Definitions

Fever is a common complaint in children seeking medical care. We define *fever without source* (FWS) as fever for *less than a week* without adequate explanation after a thorough history and physical examination. Although higher temperature (>39 °C) has been classically associated with a higher risk of bacteremia, evidence is lacking whether this is supported in the post-conjugate vaccine era. Specific guidelines for the management of infants and children with FWS have been published.

Fever of unknown origin (FUO) refers to a febrile illness lasting for *more than one week* with no apparent diagnosis after an initial evaluation that includes a detailed history, physical examination, and an initial laboratory assessment. FWS can progress to FUO if it lasts for more than a week although most febrile illnesses either resolve before a diagnosis can be made or develop distinguishing characteristics that lead to a diagnosis within the first 7 days.

FUO must be differentiated from *recurrent fever* which refers to patients with three or more episodes of unexplained fever (regardless of its duration) in a 6-month period, each of them occurring at least 7 days apart. When duration between episodes is regular it is defined as *periodic recurrent fever*. Some patients with FUO may present with recurrent fever.

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2.2 Causes

The majority of children with fever have a self-limited viral infection, most commonly acute upper respiratory tract infections. Repeated febrile episodes are frequent among healthy children attending kindergarten and again these are usually caused by viral infections.

Nowadays, the majority of children diagnosed with FUO remain etiologically undiagnosed after a complete study (51%). The second most frequent group of children with FUO comprises a heterogeneous group named "noninfectious inflammatory diseases" which represent the second cause of FUO (22%). Infectious diseases are currently only the third cause of FUO (16%), reflecting an improvement in diagnostic techniques that lead to an early diagnosis rather than changes in disease incidence rates [1].

After an infection has been excluded, rheumatic illnesses and malignancy must also be taken into account in the differential. Table 2.1 summarizes the main causes of FUO in children.

Failure to thrive, infections by unusual pathogens, repeated or complicated infections, granulomatous inflammation and/or severe autoimmunity, should raise the suspicion of an underlying primary immunodeficiency. In the early 1990s, the Jeffrey Modell Foundation (JMF) developed the ten warning signs of primary immunodeficiency to ensure an early diagnosis of these rare disorders. This set of ten warnings signs is being currently reviewed into more specialty-oriented signs (specific for hematology, oncology, pneumology, and so on), but these have not been endorsed yet. Thus, currently, if a child meets two or more of the 10 JMF

Table 2.1 Etiologies of FUO in children

Generalized infections
Brucellosis, cat scratch disease, leptospirosis, malaria, mycobacterial including tuberculosis, salmonellosis, toxoplasmosis, tularemia, viral infections (CMV, EBV, adenovirus, hepatitis viruses, enteroviruses, arboviruses, HIV)
Localized infections
Bone and joint, infective endocarditis, intraabdominal abscess, hepatic infection, upper respiratory tract infection, urinary tract infection
Primary Immunodeficiencies (manifesting with infections/inflammation/autoimmunity)
Hemophagocytic lymphohistiocytosis
Rheumatologic diseases
Autoimmune diseases
Autoinflammatory diseases
Immune dysregulation
Neoplasms
Leukemia, lymphoma, neuroblastoma, hepatoma, sarcoma, atrial myxoma
Others
Central nervous system dysfunction, diabetes insipidus, drug fever, factitious fever, familial dysautonomia, hemophagocytic lymphohistiocytosis, immunodeficiency, infantile cortical hyperostosis, inflammatory bowel disease, Kikuchi-Fujimoto disease

warning signs, a referral to a clinical immunologist for evaluation is mandatory. Of special interest is the detection of a form of primary immunodeficiency named hemophagocytic lymphohistiocytosis (HLH) [2], an inflammatory disorder that can be triggered by infections, neoplasms, or rheumatic diseases. HLH manifests as persisting fever and progressive hepatosplenomegaly and cytopenias can rapidly worsen patient's condition and even lead to death if undiagnosed.

2.2.1 Autoinflammatory Diseases and Immune Dysregulation

Autoinflammation is a term proposed in 1999 by Dan Kastner to describe a group of patients with unexplained recurrent inflammation neither associated with infection nor oncological disease. This term was defined as opposed to autoimmunity, since autoantibodies are usually not detected in these patients [3].

Later, *gain of function* mutations in *NLRP3*,a component of an intracellular multiprotein complex known as inflammasome, were found to be one of the causes of these diseases. These pathogenic mutations in *NLRP3* produced an overexpression of IL-1b, the pivotal cytokine in autoinflammation.

Over time, the boundaries between autoinflammation and autoimmunity have proven to be blurred. Defects in the innate immune system were described in diseases previously considered as pure autoimmune such as lupus, and currently we refer to them as a spectrum of immunological diseases with a predominant component of autoinflammation or autoimmunity [4].

In addition, some of the newly described autoinflammatory conditions, such as ADA2 deficiency (DADA2), associate a certain degree of immunodeficiency [5, 6]. That is why the term immune dysregulation is preferred by us to autoinflammation [7].

As genetic techniques have progressed, the number of autoinflammatory diseases (AD) with an identified pathogenic mutation has increased. These disorders are known as monogenic AD and include different diseases with a described inherited pattern such as Familial Mediterranean fever (FMF), hyperimmunoglobulin D syndrome (HIDS), TNF receptor-1 associated periodic syndrome (TRAPS) and cryopyrin-associated periodic syndromes (CAPS).Currently, most of the patients with a suspected autoinflammatory background remain genetically undiagnosed. Polygenic AD include diseases such as systemic Juvenile Idiopathic Arthritis (sJIA), Behçet Disease and *Periodic Fever with Aphtous Stomatitis, Pharyngitis, and Adenitis* (PFAPA) syndrome. PFAPA syndrome is the main non-infectious cause of recurrent fever.

According to their predominant mechanism of inflammation, monogenic AD have been classified into 6 groups: (1) AD mediated by activated inflammasomes and IL-1β production pathways, (2) Abnormal protein folding or unstable protein structure, (3) AD mediated by the NF-kβ pathway, (4) AD mediated by the type I interferon pathway, (5) AD mediated by the type I interferon pathway, and (6) AD mediated by unknown mechanisms [8].

Once infection and malignancy seem unlikely, it is important to keep AD in mind since genetic tests are available for the diagnosis and specific treatments are available depending on the pivotal cytokine that is involved. In addition, these patients must be carefully followed up to avoid or early detect severe complications such as hearing loss in CAPS or amyloidosis in FMF. Genetic counseling is also mandatory in these severe diseases.

2.3 Evaluation

The cause of fever should promptly be evaluated, especially in infants, due to the risk of serious infections. A detailed history and physical examination are essential. The history should include details about the fever, associated complaints, and exposures (e.g., to ill contacts, animals, insects, travel, drugs). The patient should be examined while febrile.

Table 2.2 summarizes recommended initial and subsequent tests for FUO in children.

Normal erythrocyte sedimentation rate and C-reactive protein decrease the likelihood of an infectious or inflammatory cause.

Absence of tachycardia and nonspecific symptoms, such as malaise or discomfort, in a patient with high fevers, rapid defervescence without diaphoresis, failure of the temperature curve to show normal diurnal variation, extreme hyperpyrexia, discrepancies between temperatures recorded by the patient or by caregivers, and those obtained by health practitioners suggest a factitious fever.

The increase in ferritine levels above 10,000 ng/mL in a child with a consistent clinical picture can suggest of sJIA with/without macrophage activation syndrome (MAS). Differential diagnosis with HLH, malignancy, hepatic diseases, and/or repeated blood transfusions should be done.

In patients with FUO in whom the findings from the initial workup and imaging studies are nondiagnostic, PET/CT examination may be preferable to radiolabeled leukocyte studies because of its high sensitivity and lower cost [9].

2.4 Management

Understanding molecular mechanisms in AD allows for the use of targeted treatments. Most of the AD mediated by activated inflammasomes and IL-1β production pathways are highly responsive to anti IL-1 therapies, such as the recombinant IL-1-receptor antagonist anakinra, the monoclonal antibody against IL-1b canakinumab, and the recombinant IL-1R fusion protein rilonacept. However, patients with *NLRC4*-associated syndromes do not fully respond to IL-1b blockade, partially because of the high expression if IL-18 in their blood, whereas treatment with recombinant IL-18-binding protein may produce a dramatic improvement. Colchicine is the preferred treatment for FMF, whereas IL-1 inhibitors are effective in colchicine-resistant FMF.

Table 2.2 Recommended evaluation in FUO in children

Initial evaluation (in all children with FUO)
Complete blood count and peripheral smear
Erythrocyte sedimentation rate and C-reactive protein
Serial aerobic and anaerobic blood cultures
Urinalysis and culture
Chest radiograph
Tuberculin skin testing (TST) and interferon gamma release assays (IGRAs)
Serum electrolytes, blood urea nitrogen, creatinine, and hepatic aminotransferases, ferritine, immunoglobulins (IgG, IgA, IgM), LDH
Combination antigen/antibody HIV immunoassay
Abdominal ultrasound
Additional diagnostic tests suggested by the history, physical examination and initial evaluation
Viral and bacterial serologies and PCR
Stool cultures and/or examination for ova and parasites (1)
Electrocardiography and echocardiography (2)
Calprotectin stool test, digestive endoscopy (3)
Anti-streptolysin (ASLO), rapid streptococcal antigen test and/or throat culture for group A beta-hemolytic streptococci (4)
Antinuclear antibody (ANA), C3 and C4 (5)
Anti-neutrophil cytoplasmic antibody (ANCA) (6)
HLA-B51 (7)
Genetic tests for monogenic autoinflammatory diseases (8)
Bone marrow aspirate (9)
Bone scintigraphy and/or magnetic resonance imaging (10)
Positron emission tomography (PET) scans (11)

(1) In children with gastrointestinal complaints, loose stools or recent international travel; (2) suspected vasculitis (Kawasaki disease, other vasculitis), endocarditis or pericarditis; (3) suspected inflammatory bowel disease; (4) suspected rheumatic fever; (5) suspected connective tissue disorders (lupus, juvenile dermatomyositis, Sjögren syndrome, systemic sclerosis, mixed connective tissue disease); (6) suspected ANCA-associated vasculitis; (7) suspected Behçet disease; (8) suspected monogenic autoinflammatory diseases; (9) suspected malignancy or macrophage activation syndrome/hemophagocytic lymphohistiocytosis; (10) suspected malignancy, osteomyelitis; (11) fever persists despite previous study

Many of the NF-kβactivation disorders respond well to TNF inhibition. JAK inhibitors are currently under study in patients with interferonopathies, and other types of immune dysregulation, who usually exhibit minimal response to IL-1 and TNF blockage.

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PFAPA: Periodic Fever, Aphthous Ulceration, Pharyngitis, Adenitis

3

Jeffrey Chaitow

3.1 Introduction

In 1987, Marshall et al.—investigators from the Department Paediatrics, Division of Immunology and Infectious Diseases at Vanderbilt University in Nashville and from the Department of Paediatrics, Division of Cellular Immunobiology at the University of Alabama Birmingham—described a syndrome of periodic fever which resembled the neutropenic phase of human cyclic neutropenia in its clinical presentation. They ruled out the diagnosis of cyclic neutropenia with standard haematologic testing and noted a much more benign course of this newly described condition than the previously described cyclic neutropenia [1].

3.2 Historical Description

Two separate papers by Hobart Reimann entitled "Periodic Disease" were published 40 years earlier in 1948 and 1949 [2, 3]. Reimann however in his second periodic disease paper had described a collection of different diseases with periodicity as the unifying characteristic. The paper was titled "Periodic disease" with the subtext "Periodic fever Periodic Abdominalgia Cyclic Neutropenia Intermittent Arthralgia Angioneurotic Edema Anaphylactoid Purpura and Periodic Paralysis" [3].

This paper clearly describes a very heterogeneous collection and largely different from Marshall's syndrome although some of the 50 cases collected in the 1949 paper may indeed have been that of PFAPA.

Hobart Reimann in his paper comments "The name periodic disease was proposed to embrace the conditions in a newly established symptom complex, but it

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appears that periodicity of disease was known to the ancients and was ascribed to the influence of solar and lunar cycles" [3].

> "Knowledge of its cause has not progressed much further. Infectious, allergic, endocrinologic, epileptic or migrainous influences have been held responsible."

Reading through Reimann's second paper [3] in which 50 cases were collated it is clear that most do not have PFAPA. In 1 patient, the periodic fever occurred three times weekly for 34 years and in several others, the description of multiple family members' serositis and genetic racial background are more typical of Familial Mediterranean Fever.

We have certainly made significant progress following Reimann's conclusion in 1949. "Until further knowledge is attained, it is simplest to regard periodic disease as a manifestation of a rhythm of life".

3.3 Initial Marshall Syndrome Cohort

3.3.1 Clinical Characterisation

Marshall and his colleagues identified a similar pattern in 12 children from two major referral centres. They noted that the attacks were characterised by abrupt onset of fever associated with malaise, chills, aphthous stomatitis, pharyngitis, and headache with concomitant tender cervical lymphadenopathy.

They describe the episodes occurring at 4–6 week intervals, with the children being observed over a number of years. They also noted that the episodes resolved spontaneously without treatment within a 4–5 day typical time frame.

None of the patients were identified as being atopic, they had all been fully immunised and none had any significant co-morbidities.

A prodrome was reported in 5 of the 12 children. Two of the children had a prodrome of stomatitis and 1 of pharyngitis. One child had pallor and another an erythematous generalised rash.

During the febrile episodes, five patients were noted to have transient splenomegaly.

As this was described as "a new syndrome", they sought to exclude other known autoimmune and auto inflammatory disease. They therefore commented particularly on the absence of other associated features such as arthralgia, conjunctivitis, oedema, genital lesions or specific neurologic signs—other than the symptom of headache.

3.3.2 Laboratory Features

Laboratory testing documented a mild leucocytosis and elevation of the erythrocyte sedimentation rate during the attack as the only identifiable significant clinical laboratory abnormalities.

The immune serologic testing performed at the time was negative other than one patient who had a markedly elevated serum IgE and one with a positive antinuclear antibody. Two of the patients had IgD measured and it was normal. The syndrome of hyperimmunoglobulinaemia D and periodic fever had been described by Ver de Meer et al. [4] and Reeves and Mitchell [5] 2 years earlier.

3.3.3 Natural History

Marshall and colleagues noted the condition was of relatively early age onset with the majority of children being less than 5 years old when first symptoms were noted. They commented that the children grew normally and that they were not unusually susceptible to outside infection as are children with cyclical neutropenia.

They noted the syndrome was sporadic, was much more common than the previously described differential diagnosis of cyclic neutropenia.

There was an average duration of follow-up of 3.9 years although the range varied from 1 to 15 years and they also noted significantly that the intervals between cycles seemed to increase as the children aged.

3.3.4 Therapy

Although the attacks resolved spontaneously in 4–5 days, they could be dramatically aborted by a short course of prednisolone in the three patients in whom it was trialled-particularly effective if started at the very onset of symptoms. They also noted a failure of adequate response to non-steroidal anti-inflammatory medication tried in two documented patients and all the illnesses were refractory to any antibiotic intervention.

A summary of their findings is tabulated below in Table 3.1 [1].

Table 3.1 Signs and symptoms associated with syndrome of periodic fever

	Patient											
	1	2	3	4	5	6	7	8	9	10	11	12
Malaise	+	+	+	+	+	+	+	+	+	+	+	+
Chills	+	+	+	+	–	+	+	+	+	+	+	–
Stomatitis	+	–	+	–	+	+	–	+	+[a]	+[a]	+	+
Pharyngitis	+	+	+[a]	+	+	+	+	+	+	–	–	–
Headache	+	–	+	+	+	+	+	–	+	+	+	–
Cervical adenopathy	+	+	–	+	+	–	–	+	+	–	+	+
Nausea and vomiting	+	–	+	–	+	–	–	–	+	+	+	–
Abdominal pain	–	–	+	+	+	–	–	–	+	+	+[a]	–

[a]Prodromal

3.3.5 Ethnicity

The 12 children originally described by Marshall and colleagues were all Caucasian 7 boys and 5 girls. They commented that none were of Mediterranean descent though the diverse ancestry included European and American Indian stock.

3.3.6 Recommendations

They recommended that given the relatively benign nature of this condition in their 12 patients a diagnosis of this condition was particularly important to reduce unnecessary hospitalisation and expensive investigation as well as being necessary in placating patients' parents and physicians.

3.4 Subsequent Cohort of PFAPA

3.4.1 Diagnostic Criteria

In a letter to the editor of the Pediatric Infectious Disease Journal—September 1989, Marshall et al. presented the acronym PFAPA and a set of diagnostic criteria for the syndrome [6]. In January 1999, Thomas and Edwards presented a revised set of diagnostic criteria for PFAPA published together with the presentation of 94 children with PFAPA.

The criteria are listed below in Table 3.2.

Over the next 40 years, many papers have described larger cohorts of PFAPA, the largest—301 patients—relatively recently being described in 2014 by Michael Hofer et al., an International collaboration within the periodic fevers working party of the Pediatric Rheumatology European Society (PReS) [8].

Since there are no absolute diagnostic criteria for the diagnosis of PFAPA, the inclusion criteria for Hofer's study was "the diagnosis of PFAPA made by an experienced paediatric rheumatologist participating in an international working group on periodic fever syndromes".

Table 3.2 Diagnostic criteria for Marshall's/PFAPA syndrome [7]

1. Regularly recurring fevers with an early age of onset (<5 years of age)
2. Constitutional symptoms in the absence of upper respiratory tract infection with at least one of the following clinical signs:
(a) Aphthous stomatitis (b) Cervical lymphadenitis
(c) Pharyngitis
3. Exclusion of cyclic neutropenia
4. Completely asymptomatic interval between episodes
5. Normal growth and development

Fifteen centres cooperated with the study which resulted in 301 reported patients. Only 42% (132 out of 301 patients) had all clinical features of fever, pharyngitis, cervical adenitis and oral aphthosis.

3.4.2 Age of Onset

As in the original Marshall study there was a slight predominance of males 1.15–1. There was a much younger median age of disease onset of 1.7 years (0.1–12) with a comparatively young median age at diagnosis of 4 years, almost certainly due to the increasing familiarity of this condition by clinicians.

The patients were separated into the essential sign of fever combined with additional signs totalling one, two, or three features of pharyngitis, cervical adenitis, and oral aphthosis. The patients with fewer signs tended to have a younger disease onset than the patients who had one additional feature in addition to the fever.

3.4.3 Symptoms

Common additional symptoms included headache, abdominal pain, arthralgia, abdominal pain and myalgia. In the large cohort of 301 patients, positive family history was noted in 81 of 301, mainly including episodes of recurrent fever (47/81) and less commonly, recurrent tonsillitis (15/81).

3.4.4 Genetics

PFAPA had been diagnosed in 11 out of 301 patient's family members and FMF in 8. The racial origin of patients reflected the ethnic mix of the participating centres and in the author's assessment reflected similar proportions to that of foreigners living in the particular European centres. No one particular or specific ethnic background was shown to have a prominent weighting.

3.4.5 Laboratory Features

As distinct from the earlier study of Marshall, most patients had a CRP measured as well as an ESR and this showed consistently a striking early rapid increase during the period of fever; CRP was >50 mg/l in 131 patients and >100 mg/l in 77 patients in whom it was measured during a flare.

The trough level in almost all patient fell to a median value of 5 mg; in 12 patients however the level was still mildly elevated at >10 mg/l. The consistent response to steroids was noted with resolution of the fever in 63% of patient in whom this was tried (93 of 147 within a short time frame) 32% of patients were partially responsive and 5%—8 patients, were designated non-responsive to steroids.

Many patients in this Hofer et al. study particularly those of older age onset had genetic testing performed to exclude monogenic auto inflammatory disease but there was no specific exclusion criteria protocol and it was left to the individual centre to perform the testing.

Forsvoll as part of his PhD thesis performed a population-based study in which all children in South Rogaland Norway diagnosed with PFAPA during 2004–2010 were evaluated clinically, and the parents interviewed.

Forty-six children (32 boys) were diagnosed with PFAPA. The median age of onset was a much younger 11.0 months. The incidence of PFAPA was estimated to be 2.3 per 10,000 children up to 5 years of age [9].

3.5 Clinical Manifestations of PFAPA

3.5.1 Fever

PFAPA is known to be to be the most regularly cycling of the periodic fevers in children. The fevers often have such predictable regularity that families can plan events around the probable future flares although this is not true of all patients. The fevers are of abrupt onset and tend to abate rapidly at the end of the cycle—many parents of younger children will note a prodrome of irritability sore throat or change in temperament. Prolonged fevers >7 days or very irregular fever patterns should prompt consideration of alternative diagnoses.

Marshall described the fevers as typically lasting 5 days and having a symptom-free interval that lasted an average of 4.5 weeks with a range of 2–9 weeks. His group noted that the asymptomatic interval tended to increase with age.

The level of fever was not defined in Marshall's original paper but described as being of abrupt onset and characteristically reaching 40–41 °C. Other studies have used 38–38.9 °C with the proviso that the fever is undifferentiated, that is, no other obvious explanation [10, 11].

The fever pattern tends to wane if not completely disappear over a period of many years. In addition to the decreased frequency of fevers, there is a concomitant increase in interval between the episodes and each episode shortening in duration. This was demonstrated in a long-term study of US patients in 2011 with a follow-up ranging from 12 to 21 years (59 of the original 94 patients) [14]. Overall, 50 of the 59 patients had complete resolution of symptoms, yielding a mean illness duration of 6.3 years. Nine patients continued to have persistent symptoms at follow-up, for a mean duration of 18.1 years.

In subjects with persistent PFAPA, the duration of the febrile episodes was reduced from a mean of 3.6 days at diagnosis to 1.8 days at follow-up. In addition, the symptom-free interval between episodes markedly lengthened from 29 to 159 days.

3.5.2 Aphthous Stomatitis

Ulcers most commonly present with shallow ulcers in the buccal mucosa and pharynx. They are usually small <5 mm and non-clustering. They last from 3–5 days and heal without scarring.

Stomatitis was described in 9 of the original 12 patients in Marshall's series and in 2 of the patients was reported as a prodrome 24 hours prior to the onset of the fever.

Aphthous stomatitis is a sign that is not always confined in duration to the PFAPA episodes and some children with very frequent attacks do not recover completely from their ulcers between attacks.

3.5.3 Pharyngitis

Pharyngitis consists of an erythematous pharynx with tonsillar enlargement. Most authors in various studies have not defined whether the tonsillitis is exudative.

Pharyngitis was described in 9 of the original 12 patients in Marshall's series—the same number as were diagnosed with stomatitis; 6 of the patients having both signs.

Negative bacterial and viral cultures from the pharynx and tonsils are expected as "no other cause for the fever" was listed as a criterion in Marshall's original paper and remains an essential exclusion criterion [1].

One does need to acknowledge however that a baseline level of carriage of Streptococcus exists to varying degrees in different populations. In a United States cohort of patients with PFAPA, 29 of 284 throat cultures yielded Group A Streptococcus [7]. Antibiotic treatment in this situation of patients colonised with Streptococcus however would not affect the fever.

3.5.4 Adenitis

Cervical lymphadenitis is one of the major disease features with almost 90% of patients having this manifestation in some series, and 66%—8 of the 12 patients in Marshall's original description. Enlarged nodes are moderately tender, rapidly appearing and regressing, often bilateral, not exceeding 5 cm in diameter, neither red nor warm, and never fluctuant.

If more generalised lymphadenopathy is found, it should warrant searching for a more significant pathology.

Transient splenomegally was reported in Marshall's original paper [1] (5 of the 12 children) but hepatosplenomegally is not considered part of the PFAPA Syndrome.

3.5.5 Non Classic Symptoms

Although not part of the original diagnostic criteria [7] associated symptoms of being constitutionally unwell are not infrequent accompaniments.

These may include non-specific abdominal pain (but not serositis or peritonism) in up to 65% of children, arthralgia in up to to 42% (but no joint swelling), vomiting in a similarly reported proportion and headache in up to 65% [7–9, 11].

3.6 Exclusion Criteria

3.6.1 Cyclic Neutropaenia

As noted from the first description of Marshall et al., PFAPA resembled the neutropaenic phase of human cyclic neutropenia in its clinical presentation.

We now know that true cyclic neutropaenia is a rare, autosomal dominantly inherited disorder, having variable expression and an estimated incidence of one to two per million [12, 13].

Ninety percent of patients exhibit a cycle period of 21 days and cyclic neutropaenia is attributable, in at least 95% of cases, to autosomal dominant mutations in the elastase gene (*ELANE*) on chromosome 19p13.3 [12, 13].

Documenting neutrophils in the normal range three times weekly for up to 6 weeks between two subsequent febrile episodes is considered sufficient to rule out cyclic neutropenia in patients evaluated for PFAPA.

Monogenic auto inflammatory diseases are usually clinically distinguishable from PFAPA—and thus genetic testing is indicated where atypical fever patterns, serositis, or incomplete response to steroids makes PFAPA unlikely.

Summary of Diagnostic criteria Table 3.3**.**

3.7 Aetiology and Pathogenesis

Sarah Long in her paper published in 1999 notes “I conclude that PFAPA syndrome walks like dysregulation of cytokines and sounds like an infection” [18].

The scoring system proposed in her paper is calculated to weigh up infection vs. immune dysregulation as an underlying cause for PFAPA.

The periodicity of fever with wellness in between, the response to steroids but not antibiotics, and the long duration of the syndrome without any long term health sequelae are all against infection.

In contradistinction however the response to tonsillectomy, the ethnic diversity of the patients and the early age of onset are factors which would support an infectious cause.

The PFAPA syndrome does not have a known genetic cause. PFAPA may be caused by oligogenic or complex inheritance of variants in many genes, interacting with nongenetic factors [19].

Table 3.3 Diagnostic criteria for PFAPA modified from Harel et al. [10]

Criteria	Marshall et al. [6]	Thomas et al. [7]	Garavello et al. [32]	Feder and Salazar [11]	Vanoni et al. [17] (No = ranking)
Onset <5 years of age	✓	✓	✓	N.S	Ranked 22
Characteristics of fever	Abrupt onset	Not specified	Abrupt onset	>38.9°	Not specified
Frequency of episodes	Regular	Regular	Regular	≥6 every 2–8 weeks	1
Duration of episodes	~5 days		~5 days	≤10 days	10 3–5 days
Constitutional symptoms	✓	✓	✓		
Clinical findings (≥1 of the following:)					
Aphthous stomatitis	✓	✓	✓	✓	2
Pharyngitis	✓	✓	✓	✓	6
Cervical lymphadenitis		✓	✓	✓	4
Acute phase reactants	✓				7
Asymptomatic intervals	✓	✓	✓	✓	5
Exclusion of URTI	✓	✓	✓		27
Exclusion of cyclic Neutro	✓	✓	✓	✓	15
Other exclusions	✓		✓	✓	
Benign long-term course	✓				
Response to corticosteroid			✓		3
Normal growth and development	✓	✓	✓		8

The numbers in column 6 Vanoni et al. [17] refer to a scaled weighted ranking of importance by clinicians in Delphi survey

It is currently thought to result from some degree of immune dysregulation. Transient rises in gammaglobulins, IgM, IgG and IgA may occur, with one study by Kovacs showing increased plasma IgD levels (322.2 ± 29.2 U/l) were detected in all of 14 patients in this small series of patients [20].

Marshall's original group and most subsequent large cohort studies have required the exclusion of the hyper IgD Syndrome before enrolling patients for study in a diagnostic cohort.

The study of whole blood gene expression profiling could clearly distinguish PFAPA flares from asymptomatic intervals [20]. In association with high fevers,

other cytokines including interferon gamma, TNF alpha, IL1 beta and IL6 have been observed to be elevated [21]. There have also been reports of over-expression of complement and interferon induced genes during an attack.

The increase in IL-1 during PFAPA flares demonstrated in two different studies suggests a possible role in the pathogenesis of PFAPA febrile attacks, as well as the use of IL-1 inhibition in treating PFAPA [21, 22].

There is an increase of S100A8/A9 and S100A12 in the febrile phase of PFAPA that seems to normalise in the afebrile phase [23]. This may help in differentiation from untreated FMF where serum amyloid A often remains elevated between fever episodes.

These findings indicate that there is an activation of both the innate and the adaptive immune system in PFAPA with a Th1 differentiation of CD4+ cells during febrile episodes.

A study in 2016 by Tejesvi et al. [24] used next-generation sequencing technology to investigate the bacterial microbiota of the tonsils of 30 PFAPA patients and 24 controls. They noted that the microbiota of the tonsils removed from PFAPA patients differed significantly from those of the controls and postulated that the tonsillar microbiota may play a role in triggering the inflammatory processes that lead to symptoms of PFAPA.

This ties in with the proposed model of Stojanov et al. in which microbial triggers activate a cascade beginning with the innate immune system and ultimately recruiting activated T cells to the periphery. [22].

3.8 Genetics

Familial clusters of PFAPA have been described in Europe [25], Japan [16], and the USA [26].

Whole exome sequencing—a comprehensive genetic study on 68 individuals from 14 families did not find a specific gene suggesting that PFAPA results from oligogenic or complex inheritance of variants in multiple disease genes and/or non-genetic factors [19, 27].

3.9 Treatment

There is no consistency in the best approach to treatment of the PFAPA although it is almost uniformally noted to have a rapid response of the fever to oral steroids.

Marshall in 1987 described three children who had dramatic symptomatic relief from short courses of prednisone, beginning with 40 mg/day (their weights were not described in the paper). This was particularly effective if started at the first sign of an impending attack.

3.9.1 Glucocorticoids

Prednisolone is the steroid that has been given most frequently in studies and used by most experienced clinicians.

In 2006, Tasher et al. reported termination of the febrile episode in 51 out of 54 children after a single dose of prednisone with a mean dosage of 0.59 mg/kg [28].

The recommended dose of prednisolone is somewhere between 0.5 and 2 mg/kg immediately at the onset of symptoms and often a single dose will suffice.

The study by Yazgan comparing the low dose prednisolone 0.5 mg/kg and high dose 2 mg/kg dose in 41 patients showed no difference in efficacy between these two dosage regimens [15]. The effectiveness of the treatment was determined by the time needed to reduce the fever and the effect on the duration between the initially treated and subsequent attacks. The patients were re-examined 24 h after the steroid treatment.

A second dose 24 h later may be necessary in some patients if the symptoms are ongoing.

Response to corticosteroids was the third highest ranked diagnostic variable amongst 110 expert physicians in a recently published international Delphi survey for the development of new classification criteria for PFAPA [17].

Although Prednisolone is effective in terminating the episode, there has been some suggestion that in some patients, it may shorten the interval between episodes; this group may be between 20% and 50% of the patients in some studies [28, 29].

As in Marshall's original Paper, there is a poor response to NSAIDs; although NSAID's may reduce the fever, they do not abort the other symptoms, the syndrome is by definition antibiotic unresponsive.

3.9.2 Tonsillectomy

In 2007 and 2009 two randomized clinical trials using tonsillectomy for the therapy of PFAPA were published.

Renko et al. conducted a prospective, randomized, controlled trial in 26 children with well-defined PFAPA [30].

Six months after randomization, all 14 children in the tonsillectomy group and 6 of 12 children in the control group were free of symptoms. Tonsillectomy was subsequently performed on five of six of the patients in the control group who still had symptoms after 6 months and they also had symptom resolution.

Hofer however criticised the study in a subsequent letter to the journal noting that half of the patients did not meet the previously described diagnostic criteria because they did not present at least one of the main symptoms accompanying the fever. He also noted that half the control patients in the study of Renko showed disease remission within 6 months of follow-up which was not consistent with other studies of this syndrome [31].

Garavello et al. reported on 39 children with PFAPA syndrome who were randomized to either adenotonsillectomy (surgery group; $n = 19$) or expectant management (control group; $n = 20$).

All patients prospectively recorded all PFAPA episodes and were evaluated clinically every 3 months for 18 months after randomization.

Sixty-three percent of patients in the surgery group and 5% in the control group experienced complete resolution of symptoms ($P < 0.001$) [32].

Several other groups have subsequently reported on the success of tonsillectomy in children with PFAPA [33, 34] and the data have been summarized in a Cochrane systematic review [35].

In the Delphi survey of 2018 previously mentioned above [17] response to tonsillectomy only ranked as the13th most important diagnostic criterion amongst respondents. The authors did however comment that the response to tonsillectomy is probably not a desirable feature to support the diagnosis of PFAPA, since response to tonsillectomy is also found in non-PFAPA recurrent tonsillitis and it is important to establish a diagnosis prior to surgical referral.

3.9.3 Cimetidine

Cimetidine is anecdotally efficacious in some patients. The PFAPA syndrome resolved in 8 of 28 patients (29%) treated for 6 months with cimetidine [36]. No randomized, controlled trials of cimetidine prophylaxis have been performed for PFAPA.

Cimetidine may increase the interval between attacks or decrease the severity of each episode. In some children it has been reported to result in resolution of PFAPA episodes. Cimetidine is usually given at 20–40 mg/kg/day in divided doses every 12 h. If cimetidine reduces the frequency of recurrent fevers or eliminates them altogether, an attempt to discontinue the drug is appropriate after 6–12 months of continuous use. Prednisolone may still need to be given for breakthrough episodes.

In a 2016 survey completed by 277 US paediatric subspecialty physicians, 124 paediatric rheumatologists, and 153 paediatric infectious disease specialists, 48% report that they have used cimetidine in the treatment of PFAPA but only 8% use it as their most commonly prescribed treatment; only 19% rated it as effective or very effective [37] (Table 3.4 below).

3.9.4 Colchicine

Colchicine can be used as an alternative option for prophylaxis in PFAPA patients.

The exact mechanism of action is unknown although one possibility is colchicine interferes with the inflammasome complex found in neutrophils and monocytes that mediates interleukin-1β (IL-1β) activation.

In the same 2016 survey, 31% of rheumatologists but only 5% of ID physicians used colchicine to treat PFAPA with only 19% ranking it as effective or very effective [37].

In a case series of nine patients with frequent PFAPA episodes defined as occurring at intervals of ≤14 days, prophylaxis with colchicine (0.5–1 mg/day) was administered [38]. All of these patients also received glucocorticoids to treat their episodes. The patients were followed for an average of 2 years on colchicine. In eight of nine patients, treatment with colchicine was associated with an increased interval between episodes (the average interval increased from 1.7 to 8.4 weeks). In

Table 3.4 Percentage of pediatric physicians who use various modalities to treat PFAPA syndrome

Medication	% Who rank the specific medication in top 3 most commonly used treatment				% Who rank treatment as most commonly used	% Who rate as "very effective" or "effective"
	All physicians	Rheumatologists	ID physicians	*P* value		
Corticosteroid	87	88	86	0.53	55	95
Antipyretics	61	59	63	0.60	29	29
Cimetidine	48	52	46	0.36	8	19
Tonsillectomy	57	45	67	<0.001	5	68
Colchicine	17	31	5	<0.001	1	19
Anakinra	6	9	5	0.19	1	–
Montelukast	6	9	3	0.07	0	3

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two patients, discontinuation of colchicine was associated with an increased frequency of episodes. This study from Israel may not translate to other ethnic groups with PFAPA as two patients were compound heterozygotes for *MEFV* mutations.

An additional Israeli study which was open label and randomized involved twice as many—18 patients with PFAPA. Patients were randomly assigned to no treatment for 6 months or observation for 3 months followed by colchicine treatment for 3 months.

The study showed that colchicine prophylaxis was effective in reducing the number of PFAPA episodes [39].

Patients in the treatment group had fewer PFAPA episodes while on colchicine therapy (4.9 ± 2.3 versus 1.6 ± 1.2 episodes per 3-month period).

Colchicine is generally safe to use in children though commonly reported side effects are mainly gastrointestinal including abdominal pain, diarrhoea, and nausea. The dose should be slowly increased over several weeks starting from 250 to300 μg/day to the desired dose to mitigate these side effects.

The concomitant use of Colchicine and CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole, grapefruit juice, erythromycin), should be avoided due to the potential for serious and life-threatening toxicity.

3.9.5 Anakinra

In a 2006 study, testing PFAPA patients during a flare increased serum levels of cytokines IL1 and IL6 was noted when compared to the control group; and a decrease in serum levels of anti-inflammatory cytokines, particularly IL-4 and IL-10 was also demonstrated [40].

A later study in 2011 showed that during PFAPA attacks, complement, IL-1-related (IL-1B, IL-1RN, CASP1, IL18RAP), and IFN-induced

(AIM2, IP-10/CXCL10) genes were significantly over expressed [22]. PFAPA flares were accompanied by significantly increased serum levels of chemokines for activated T lymphocytes (IP-10/CXCL10, MIG/CXCL9), G-CSF, and proinflammatory cytokines (IL-18, IL-6).

Based on the evidence for IL-1β activation in PFAPA flares, the authors treated five PFAPA patients with a recombinant IL-1 receptor antagonist. All patients showed a prompt clinical response [22].

3.9.6 Vitamin D

An Italian study of 25 children with PFAPA was published in 2014 looking specifically at vitamin D as a predisposing factor and an adjunctive treatment. Hypovitaminosis D was found in most children with PFAPA syndrome. It was postulated that this might be a significant risk factor for PFAPA flares. Vitamin D supplementation in this group significantly reduced the typical PFAPA episodes and their duration, the authors suggesting the role of vitamin D as an immune regulatory factor in this syndrome [41].

3.10 Into the Future

Recently—April 2018, an International Delphi survey has been undertaken amongst Paediatric Rheumatologists to define more clearly the most important diagnostic variables for clinicians to diagnose PFAPA. This is the first step of a planned process aimed to develop new classification criteria for PFAPA [17].

The ongoing follow-up to this survey will attempt to develop new classification criteria for the PFAPA Syndrome through consensus and data validation in the large data set of the Eurofever Registry.

The DELPHI method "Project DELPHI" was first described by Norman Crolee Dalkey and Olaf Helmer-Hirschberg in 1962 in a paper titled "The use of experts for the estimation of bombing requirements". The paper and study had been written in 1951 but publication was suppressed for 10 years until the original study had been declassified [42].

The paper reported that the DELPHI method was devised in order to obtain the most reliable opinion consensus of a group of experts. This was done by subjecting the experts to a series of in depth questions interspersed with controlled opinion feedback. The technique employed involved the repeated individual questioning of the experts (by interview or questionnaire) and avoided direct confrontation of the experts with one another. The hope listed in the original paper is that expert opinion consensus would be an acceptable substitute for direct empirical evidence when the evidence was unavailable.

This use of the DELPHI method was applied to the definition of the variables for the development of new classification criteria for (PFAPA).

This consisted of an open ended questionnaire sent to both adult and paediatric clinicians and researchers. Participants were asked to identify the variables thought most likely to be helpful and relevant for the diagnosis of PFAPA in current clinical practice and in research setting.

In the first survey, participants were asked to report, in an open fashion, all measures they thought to be relevant for PFAPA based on their clinical or research expertise. The question was: "Please list the variables (as many as you like) that you are currently using in your everyday clinical practice or you consider to be the most useful for the diagnosis of PFAPA. Variables to be included can be of any type: i.e. clinical features, laboratory tests, genetic analysis, etc."

Of the 92 variables identified in the first survey, 62 were selected for a second DELPHI survey.

Respondents in the second survey were asked to select from a list of variables in the first survey with the ten features they thought were most important and to rank them in descending order from most important to least important.

Eighty-eight percent (109 of 124) responded to the first DELPHI survey and 87% (141 of 162) to the second.

A ranking was then attained combining the listing of the variable (from 1 being the most important) with the number of clinicians that had selected that variable.

The five features with the highest weighting were

1. Regular Periodicity of fever
2. Aphthous stomatitis
3. Response to steroids
4. Cervical lymphadenitis
5. Return to wellbeing i.e. normal health in between flares

The highest total score was given to the regular periodicity of the fever with the single most selected variable being aphthous stomatitis (Table 3.5).

Duration of fever 3–5 days or 3–6 days received equal ranking.

The response to tonsillectomy as well as the response to steroids was ranked highly as expected. The cardinal signs were all ranked highly as was return to normal health between episodes, return of inflammatory markers to normal, and normal growth and development and long term spontaneous resolution and decreased frequency of episodes with age.

Age of onset was not ranked highly—perhaps influenced by recent studies describing older children with the condition as well as adult onset disease.

Associated features such as headache, abdominal pain, myalgia and arthralgia were included in the list of some participating clinicians but did not rank highly. Most experienced practicing clinicians would feel that these features of serositis are a stronger pointer to auto inflammatory disease such as MVK or MEFV mutation.

These survey items are now being applied in the next phase of the study testing the sensitivity and specificity on real patient data. The aim of this project is that this will result in a further tightening of the diagnosis of the PFAPA syndrome which is in itself a step towards unravelling the puzzle of this clinical condition.

Table 3.5 Top 17 of 62 variables listed by participants in Delphi survey [17]

Rank	Variable	Score	Frequency	Mean score
1	Regular periodicity	436	56	7.8
2	Aphtous stomatitis	431	77	5.6
3	Response to steroid	401	66	6.1
4	Cervical adenitis	368	72	5.1
5	Well-being between flares	299	57	5.2
6	Pharyngitis (exudative or not)	288	47	6.1
7	Increase of acute phase reactants and serum amyloid A during fever episodes	271	44	6.2
8	Normal growth/development	236	51	4.6
9	Pharingotonsillitis	228	35	6.5
10	Periodic fever 3–5 days	202	24	8.4
11	Periodic fever 3–6 days	202	23	8.8
12	Self-limiting episodes	183	35	5.2
13	Response to tonsillectomy	182	33	5.5
14	Improvement with age	160	40	4.0
15	Exclusion cyclic neutropenia/immunodeficiency	150	34	4.4
16	Normalization of acute phase reactants in well-being	146	33	4.4
17	Recurrence every 3–6 weeks	145	21	6.9

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Kawasaki Disease

4

Rakesh Kumar Pilania and Surjit Singh

Kawasaki disease (KD) is an acute and usually self-limiting medium vessel vasculitis of childhood that has a predilection to involve the coronary arteries. It is characterized by the sequential appearance of a constellation of clinical features [1]. However, none of these clinical findings is, in itself, pathognomonic of KD. Many of these clinical features can, in fact, be seen in other common febrile illnesses of children. It is for this reason that the diagnosis of KD is often considered to be a clinical challenge [2]. Approximately 15–25% of untreated patients may go on develop coronary artery abnormalities (CAAs) and this remains the major cause of morbidity, and occasional mortality, in KD [3].

4.1 History

KD was first recognized in 1961 by Dr. Tomisaku Kawasaki while working at the Japan Red Cross Medical Centre at Tokyo. He saw a 4-year-old boy with fever and a constellation of clinical features that did not seem to fit into any known clinical disease entity. By 1967, he had collected 50 such cases of *mucocutaneous lymph node syndrome* and published his series in the Japanese Journal of Allergy (Arerugi) [4]. It is remarkable that to this day, the case definition proposed by Dr. Kawasaki in 1967 has remained largely unchanged.

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4.2 Epidemiology

KD is arguably the second commonest vasculitis of childhood after Henoch–Schonlein purpura. It is a disease of young children with 80% of affected patients being below the age of 5. Peak age of onset is around 6–11 months in Japan and 2–3 years in North America. KD occurs more commonly in boys and the male female ratio is 1.3:1 [5]. Siblings can be affected in 3% of patients [6].

KD has been reported from all continents and is now increasingly being identified in many resource-challenged countries (Fig. 4.1). Although this disease is being diagnosed worldwide, the highest number of cases has been reported from the North-East Asian countries, viz. Japan, Korea, and Taiwan [7]. The current incidence of KD in Japan is more than 300 per 100,000 children <5 years (highest worldwide) [8]. Approximately 1% of Japanese children develop KD by age 10 [9]. Incidence rates from Korea and Taiwan are 194.7 and 69.5, respectively [10, 11]. Incidence of KD in Europe and the United States has plateaued and ranges from 5 to 30/100,000 children below 5. Data from North America show that there is significant ethnic variation with higher rates being reported in African Americans and Pacific islanders [7]. KD is currently being diagnosed and reported from both China and India but nationwide data are not available in these countries [12–16]. In North India, the KD incidence is 4–5/100,000 children below 5 [16].

Epidemiologic studies have shown distinct seasonality in occurrence of KD. Japan and Korea have two peaks—in June/July and December/January [17], while Taiwan has a peak in May/June [7]. In Chandigarh (India), the peak incidence is in April and October, with a nadir in February [16].

4.3 Genetics

KD is a complex disorder in which an infectious/environmental agent is believed to trigger the onset of disease in a genetically susceptible host [18]. Various susceptibility genes have been identified to have association with KD. These includes inositol 1,4,5-trisphosphate 3-kinase C (ITPKC), Caspase-3 calcium release-activated calcium modulator 1 (ORAI1), and CD 40 [19–21]. Knowledge about these susceptibility genes may provide new insights in etiopathogenesis of KD. Reports have suggested association of transforming growth factor (TGF)-β variants with development of CAAs in patients with KD [22].

4.4 Etiopathogenesis of KD

Although etiopathogenesis of KD is not clear, various epidemiological and laboratory studies have shown that an infectious agent triggers a cascade that causes the illness (Fig. 4.2). Histopathologic studies have emanated from children with KD who have died from unrelated causes [23]. The vasculitic process shows three distinct phases [24]:

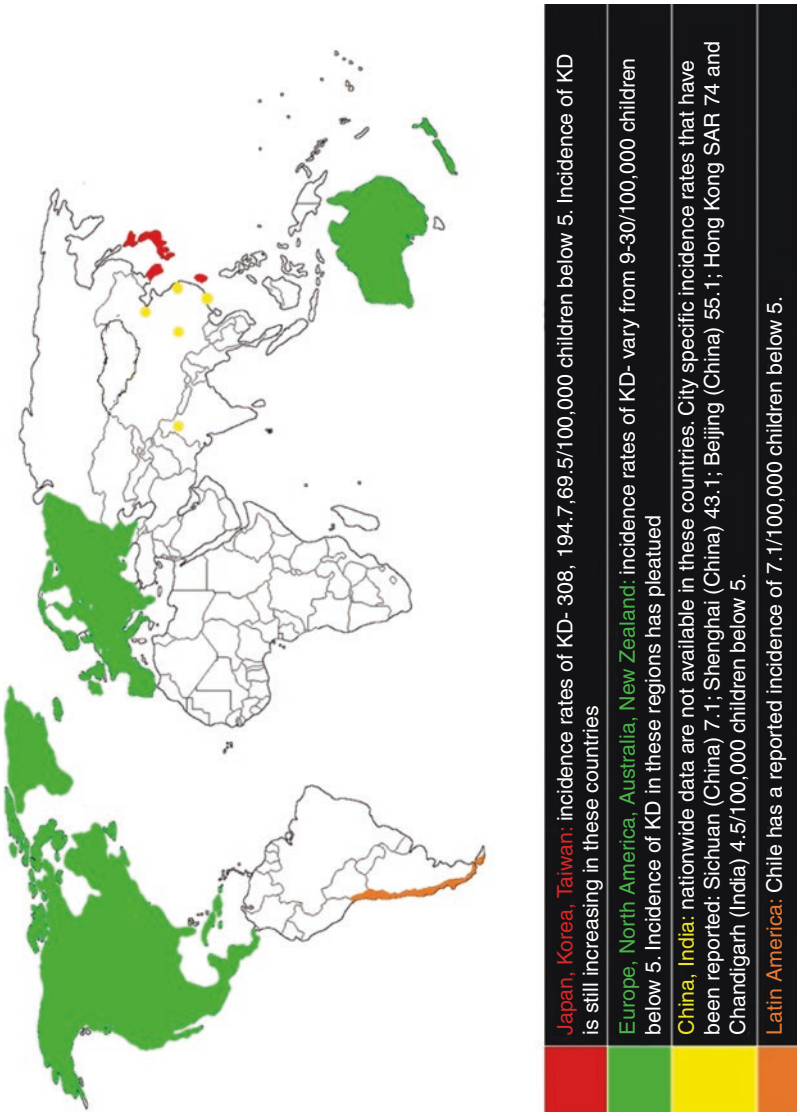

Fig. 4.1 Epidemiologic variation of KD in different areas

(a) Acute necrotizing arteritis phase: in which there is neutrophilic infiltration of intima and media.
(b) Subacute/chronic arteritis phase: in which the neutrophilic infiltrate gets replaced by lymphocytes, plasma cells, and macrophages.
(c) Luminal myofibroblastic phase: in which there is proliferation of smooth muscle cells in the media that can result in luminal narrowing [24, 25].

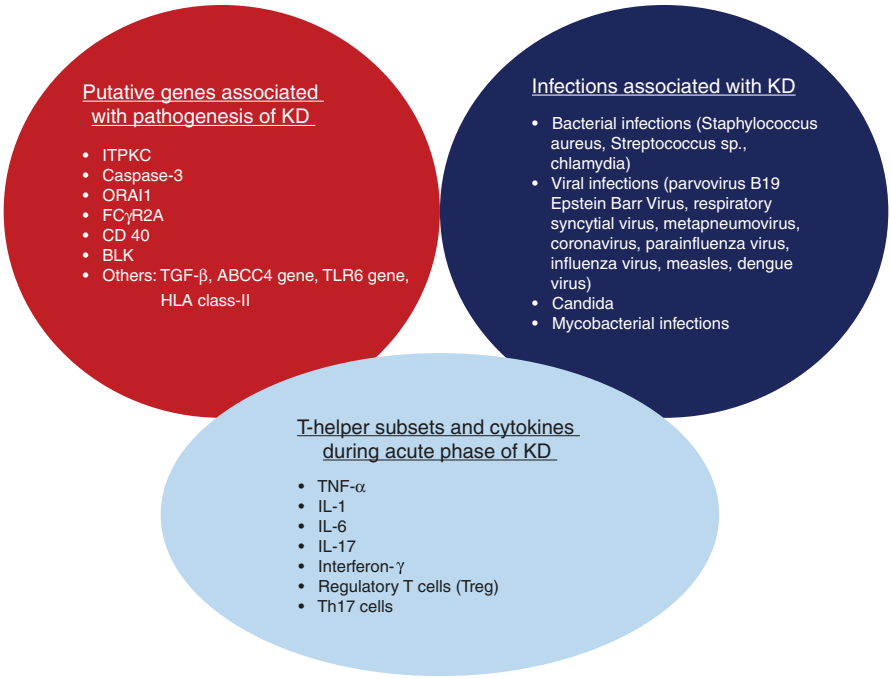

Fig. 4.2 Etiopathogenesis of KD. *Abbreviations*: *ABCC4* ATP-binding cassette sub-family C member 4, *BLK* B-cell lymphoid kinase, *FCγR2A* Fc γ receptor 2A, *HLA* human leukocyte antigen, *IL* interleukin, *ITPKC* inositol 1,4,5-trisphosphate kinase-C, *ORAI1* calcium release-activated calcium modulator 1, *TGF-β* transforming growth factor-β, *TLR* toll like receptor, *TNF-α* tumor necrosis factor

The etiopathogenesis of KD is closely linked to an infectious process. Evidence for this comes from both seasonability and clustering of cases of KD [7, 26]. The presence of febrile exanthemata and cervical lymphadenopathy, uncommon occurrence in babies below 3 months, and the rarity of cases in adults, further lends support to this hypothesis. Some of the infectious agents that have been linked to the etiology of KD are parvovirus, Epstein–Barr virus, *Staphylococcus aureus*, chlamydia, and mycobacteria. It has been hypothesized that the putative infectious trigger sets up a cytokine storm that manifests as KD [23]. Some investigators have also proposed a super-antigen theory that triggers an immune response against vascular endothelium [27].

4.5 Clinical Features and Diagnosis

Diagnosis of KD is essentially clinical. Criteria for diagnosis of KD have been updated from time to time. Currently there are two sets of guidelines—American Heart Association (AHA) guidelines (2004 [3] and 2017 [28]) and Kawasaki Disease

Research Committee guidelines (Japanese guidelines), 2002 (Table 4.1) [29]. AHA 2017 guidelines (clinical criteria) for diagnosis of KD are given in Table 4.2. Patients who fulfil the criteria are classified as having complete KD (also known as classical or typical KD), while those who do not fulfil criteria are classified as incomplete KD [28]. Principal clinical features in KD are reviewed in Table 4.3.

The clinical course of KD has three distinct phases: (a) acute febrile phase, (b) subacute phase, and (c) convalescent phase [4]. However in clinical practice, these features often overlap.

Acute phase: This phase starts with abrupt onset of high grade fever that is characteristically accompanied by significant irritability. It usually lasts for 10–14 days. Fever with marked irritability may be the initial clinical presentation of KD, especially in young infants [30]. Presence of intermittent or remittent fever is not characteristic of KD. Cough can be present in a small subset of patients but nasal catarrh is

Table 4.1 Kawasaki Disease Research Committee guidelines (Japanese Ministry of Health guidelines) for diagnosis of KD (2002) [29]

Five of the following six criteria (At least five items of 1–6 should be satisfied for diagnosis of KD. However, patients with 4 items of the principal symptoms can be diagnosed with KD when coronary aneurysm or dilatation is recognized by 2-D echocardiography or coronary angiography)
1. Fever persisting ≥5 days (inclusive of cases in whom the fever has subsided before the fifth day in response to therapy) 2. Bilateral conjunctival congestion 3. Changes of lips and oral cavity 4. Polymorphous exanthema 5. Changes of peripheral extremities 6. Acute non-purulent cervical lymphadenopathy

Table 4.2 AHA 2017 diagnostic criteria for KD [28]

Diagnosis of classic KD can be proffered in the presence of fever for at least 5 days associated with at least 4 of the 5 following principal clinical features. In the presence of ≥4 principal clinical features, particularly when redness and swelling of the hands and feet are present, the diagnosis of KD can be made on day 4 of fever also.
Principal clinical features: 1. Changes in lips and oral cavity: Erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae 2. Changes in extremities Acute: Erythema of palms, soles; edema of hands, feet Subacute: Periungual peeling of fingers and toes in weeks 2 and 3 3. Polymorphous exanthema (diffuse maculopapular, urticarial, erythroderma, erythema-multiforme like, not vesicular or bullous) 4. Bilateral bulbar conjunctival injection without exudates 5. Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral
A careful history may reveal that ≥1 principal clinical features were present during the illness but resolved by the time of presentation
Exclusion of other diseases with similar findings (e.g., scarlet fever, viral infections like measles, adenovirus, enterovirus, Stevens-Johnson syndrome, toxic shock syndrome, drug hypersensitivity reactions, systemic juvenile idiopathic arthritis)

Table 4.3 Principal clinical features in KD [28]

Clinical manifestation	Characteristics
Fever	Is typically high grade, acute onset, unremitting, without any response to antimicrobials and can associated with extreme irritability.
Extremity changes (acute)	In acute phase include erythema of palms and soles that is usually associated with edema over dorsum of hands and feet. Diagnosis of KD can be made on day 4 of illness if one of the features is redness and dorsal edema of extremities.
Extremity changes (subacute)	Periungual sheet like peeling of skin is a pathognomonic sign of KD that usually appears in the second to third week of illness.
Rash	Diffuse erythematous polymorphous rash usually appears in the first few days of illness and may be seen in >90% patients. Bullous, vesicular and petechial lesions are not seen in KD.
Conjunctival involvement	Bilateral nonexudative conjunctival injection with characteristic sparing of limbus is an important and specific clinical sign and often helps in making a clinical diagnosis. It may be seen in >85% patients.
Changes in lips and oral cavity	Erythema of lips and oral cavity with vertical lip cracking in a febrile child is an important diagnostic clue and is seen in >95% patients. Distinct oral ulcerations are unusual in KD.
Cervical lymphadenopathy	Unilateral cervical lymphadenopathy (size ≥1.5 cm) is a characteristic clinical sign of KD. This is the least common of all the principal clinical features.

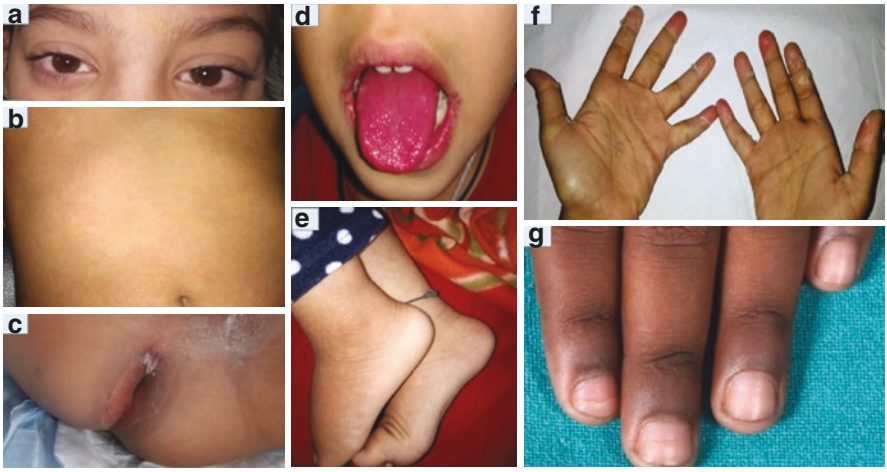

Fig. 4.3 Clinical manifestations of typical KD. (**a**) Conjuctival injection; (**b**) maculopapular erythematous rash; (**c**) classical perianal desquamation; (**d**) strawberry tongue and cracked red lips; (**e**) dorsal edema over feet; (**f**) classical periungual desquamation; (**g**) Beau's line

unusual for KD. Rash in KD is usually generalized, erythematous, polymorphic (Fig. 4.3b), but is never vesicular or bullous. Cervical lymphadenopathy (≥1.5 cm size) is usually unilateral and is often more commonly seen in the anterior cervical triangle. Cervical lymphadenopathy may be mistaken for suppurative lymphadenitis.

AHA 2017 guidelines have highlighted the importance of ultrasonogram and computed tomography (CT) for differentiation of bacterial lymphadenitis from KD lymphadenopathy. In KD, there is enlargement of multiple lymph nodes along with retropharyngeal edema while bacterial lymphadenitis is mostly associated with a single lymph node with a central hypoechoic region [28]. However, such differentiation on basis of ultrasound examination requires lot of expertise and that may not be readily available in the usual clinical setting. Oral cavity and lip changes include redness of lips with bleeding and vertical cracking, oral mucosa redness and a strawberry tongue (Fig. 4.3d). Oral ulcers are distinctly unusual in KD. Conjunctival injection is characteristically nonexudative and with typical sparing of limbus (Fig. 4.3a). Conjunctivitis with discharge is a strong pointer towards an alternative diagnosis. Edema of the dorsum of extremities is an early sign and is usually transient (Fig. 4.3e). Perianal desquamation is virtually pathognomonic of KD and is a useful clinical sign for diagnosis of the disease during the acute phase (Fig. 4.3c). Arthritis in KD is typically oligoarthritis, involving large joints and resolves without sequelae [31]. Erythema at BCG injection site is an important clinical sign during acute stage of KD and more common in infants [32]. Hydrops of gall bladder is also an important finding during acute stage. Mild pericardial effusion is a common finding on 2Dechocardiography (2DE). CAAs are usually not seen during the first week of illness.

Subacute phase: This stage usually lasts for another 2–3 weeks during which fever usually subsides. Periungual peeling is characteristically seen during this stage (Fig. 4.3f). Irritability that is prominent during acute phase subsides completely in this phase. Arthritis in KD can also develop in subacute phase. CAAs most commonly become apparent during this time. An important laboratory manifestation that is seen in the subacute phase is development of thrombocytosis and this in conjunction with periungual desquamation is very suggestive of KD.

Chronic phase: It lasts for few weeks to months; there are no symptoms during this phase and the inflammation tends to subside. Beau's lines presents as horizontal ridging over nails and first manifest at the subsidence of the subacute phase (Fig. 4.3g). This is the only clinical sign of KD that can be seen for several weeks.

4.6 Differential Diagnosis

Measles can present with similar clinical features; however, the presence of a viral prodrome, exudative conjunctivitis and Koplik spots will help to differentiate measles from KD. In measles, lymphocytic leucocytosis is usually prominent (unless there is secondary infection) while children with KD have polymorphonuclear leucocytosis. Procalcitonin levels are normal in measles but may be elevated in KD. Other infectious causes that can mimic KD include viral infections (cytomegalovirus, adenovirus, Epstein Barr virus, and enterovirus), bacterial infections (bacterial cervical lymphadenitis, scarlet fever, toxic shock syndrome, staphylococcal scalded skin syndrome, and leptospira), and systemic juvenile idiopathic arthritis. Absence of eye changes and lip changes, presence of sand paper rash, elevated antistreptolysin O titres, and a brisk response to antimicrobials are pointers towards

scarlet fever. Presence of exudative conjunctivitis, ulcerative lesions in oral cavity, exudative pharyngitis, generalized lymphadenopathy and significant running nose are certain clinical features that make the diagnosis of KD less likely [28].

4.7 KD in Special Situations

4.7.1 Incomplete KD

The diagnosis of KD is challenging and requires experience. Clinical features of KD are nonspecific and overlap with various common childhood disorders especially infections [33]. Patients who are not fulfilling clinical criteria completely are labelled as incomplete KD. In these situations, one has to rely largely on clinical assessment supplemented by laboratory parameters. Incomplete form of KD is more commonly seen in infants (especially in babies below 6 months). Approach for diagnosis of incomplete KD has been simplified in new AHA 2017 guidelines [28]. Incomplete KD should, by no means, be considered a milder form of KD.

4.7.2 Atypical KD

A patient can be said to have atypical KD if the clinical manifestations are unusual. These atypical manifestations may include arthritis [31], nephritis [34], pneumonia [35], myositis, central nervous system involvement, uveitis [36], and retinal vasculitis [37]. Common neurological findings include extreme irritability and aseptic meningitis. Rare neurological manifestations include transient peripheral facial nerve palsy (mostly unilateral) and profound sensorineural hearing loss. Vomiting, diarrhea, and transient hepatitis are common gastrointestinal manifestations [38]. Other relatively uncommon findings include jaundice, gall bladder hydrops, and pancreatitis. Genitourinary findings include urethritis which usually presents as sterile pyuria [39]. Atypical presentations of KD can pose difficult clinical problems for the attending physician.

4.7.3 KD in Infants

In infancy, and especially in babies below 6 months, KD is often a diagnostic challenge because it may present with incomplete manifestations. KD in this age group may often remain undiagnosed for several days, leading to increased incidence of development of CAAs. This group of patients also has higher intravenous immunoglobulin (IVIg) resistance [28, 30, 40, 41]. Sterile pyuria is another clinical presentation of KD in this age group and may mistakenly get treated as a urinary tract infection. The consequent delay in diagnosis can result in serious clinical sequelae [39]. Due to these reasons, KD in infants has been given special consideration in new AHA guidelines. It has been highlighted that if an infant has fever

for more than 7 days without explanation, KD should always be in list of differential diagnosis.

According to AHA 2017 guidelines KD should be considered as a clinical possibility in the following situations:

- Babies <6 months who present with fever and extensive irritability.
- Infants having prolonged fever and unexplained aseptic meningitis.
- Children presenting with longer duration of fever and
  - Culture-negative hypotensive shock.
  - Cervical adenopathy that is unresponsive to antibiotic therapy.
  - Parapharyngeal or retropharyngeal phlegmon that is unresponsive to antibiotic therapy.

4.7.4 KD in Older Children and Adolescents

KD is uncommon in older children and may often go unrecognized. Due to missed or delayed diagnosis, there is higher risk of CAAs in this age group. It may be difficult to assess CAAs by 2DE in this age group of patients because of limited acoustic window and thick chest wall [42, 43].

4.7.5 KD Shock Syndrome

Myocarditis in KD is said to be very common and may even be universal. It is not often recognized and can, at times, be severe and symptomatic. Myocarditis can develop during acute stage and manifest with unexplained tachycardia, hemodynamic compromise, or cardiovascular collapse [44]. Approximately 5% patients with KD can present with cardiovascular collapse. This entity is known as KD shock syndrome (KDSS). The shock in these patients is multifactorial and may have both cardiogenic and distributive components. The distributive shock may result from cytokine storm leading to uncontrolled inflammation [45]. Patients with KDSS are usually present to emergency room and intensive care units with shock and may be inappropriately treated for bacterial sepsis and presumed septic shock. Diagnosis of KD gets often delayed in these cases and can have devastating consequences. Differentiation between KDSS and septic shock in the early phase of clinical diagnosis is often challenging. However, 2DE should always be performed in patients with fever and shock as presence of CAAs will suggest KDSS. Differentiation of KDSS and septic shock is critical as management of both diseases is entirely different. Presence of conjunctival injection, dorsal edema, perineal desquamation, incomplete response to antimicrobials, and no microbiological evidence for infection are indicators towards KD in these patients. These patients are reported to have increased risk of having IVIg resistance, CAAs, and myocardial dysfunction [28, 46, 47]. It is said that KDSS should always be considered in children presenting with fever, cardiovascular collapse and myocardial dysfunction. KDSS has been

discussed at length in the AHA 2017 revised guidelines because of these highlighted facts [28].

4.7.6 Infection Triggered KD

Infections have been commonly considered as triggers for KD. At the bedside, it is often difficult to differentiate the clinical features of KD from that of viral exanthemata. However, if a child is having typical clinical features of the KD, the diagnosis cannot be excluded even in the presence of a documented infection. Adenovirus, coronavirus, dengue virus, enteroviruses, measles virus, respiratory syncytial virus have been reported to trigger the KD in children [23]. Toxin-mediated diseases (e.g., staphylococcal and streptococcal infection) have also been also closely associated with the pathogenesis of KD [27]. Candida infection has been linked to the causation of KD in mice models and as well as in epidemiological studies carried out on tropospheric wind patterns in Japan and Hawaii [48].

4.8 Laboratory Investigations

The acute phase is characterized by a mild normocytic normochromic anemia, polymorphonuclear leucocytosis, raised erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and usually a normal platelet count. Serum procalcitonin, that is usually thought to be a sensitive and specific marker for bacterial infection, may get elevated in KD as well. Thrombocytosis develops during the end of second week or in the third week; however it may even develop earlier [49]. Presence of thrombocytopenia during acute stage suggests either macrophage activation syndrome or thrombotic microangiopathy—this is associated with poor prognosis [28]. Progressive thrombocytosis has been correlated with development of CAAs. Urine may show sterile pyuria, secondary to urethritis and easily mistaken as urinary tract infection especially during infancy, thereby resulting in delay in diagnosis of KD [39]. It is said that KD is the commonest cause of sterile pyuria in children.

4.9 Biomarkers in KD

Diagnosis of KD is essentially clinical and there is no gold standard for confirmation of diagnosis. It is no surprise, therefore, that several biomarkers have been extensively evaluated for their role in diagnosis of this condition. Various cytokines (e.g., tumour necrosis factor-α (TNF-α), interleukin 6) have been found to be raised during the acute phase of KD and decrease promptly following IVIg administration. In patients with refractory KD or CAAs levels of TNF-α continue to remain elevated [50]. Various microarray based studies have been carried out to identify the genes associated with KD. Expression of these genes may be used as a novel diagnostic and prognostic biomarker for KD [51].

N terminal pro-B-type natriuretic peptide (NT-proBNP) is a cardiac biomarker that has recently been found to be raised in children with KD during the acute phase. Age-based nomograms for Pro-BNP are available. These are helpful in differentiation of KD from other febrile illnesses [52]. The values for Pro-BNP are comparatively higher in patients who develop CAAs as compared to patients with normal coronaries [53]. ProBNP levels also correlate with myocardial dysfunction [45].

4.10 Two-Dimensional Echocardiography (2DE)

Cardiac evaluation is an essential component in patients with KD. 2DE is an important tool for coronary artery assessment and, evaluation of cardiac structures during acute phase as well as on follow-up. However, diagnosis of KD should never be ruled out on basis of normal 2DE examination. The quality of scan obtained by 2DE is operator dependent [43].

Criteria for definition of CAAs have been given by AHA as well as by the Japanese Ministry of Health. According to the latter coronary involvement in KD is categorized on basis of absolute internal diameter of coronary artery (Table 4.4) [54]. Manlhiot et al. have proposed definition of CAAs on the basis of *Z* score which is widely accepted currently and also has been adapted by AHA 2017 guidelines (Table 4.4) [28, 55]. It is mandatory to use body surface area-adjusted '*Z*' scores for

Table 4.4 Severity of CAAs lesions: comparison between AHA 2017 [28] and Japanese Circulation Society (JCS) 2013 [54] guidelines

Terminology	AHA 2017	JCS 2013
No involvement	*Z* score <2	–
Dilatation only	*Z* score 2 to <2.5; or if initially <2, a decrease in *Z* score during follow-up ≥1 thereby suggesting that coronary artery was dilated during acute stage though diameter was within normal standards and the diameter has regressed on follow-up	–
Small aneurysm	*Z* score ≥2.5 to <5	Localized dilation with internal diameter ≤4 mm or if child is ≥5 years of age, internal diameter <1.5 times that of an adjacent segment
Medium aneurysm	*Z* score ≥5 to <10, and absolute dimension <8 mm	Dilation with internal diameter >4 mm but <8 mm or if child is ≥5 years of age, internal diameter 1.5–4 times that of an adjacent segment
Giant or large	≥10, or absolute dimension ≥8 mm	Dilation with internal diameter ≥8 mm or if child is ≥5 years of age, internal diameter >4 times that of an adjacent segment

grading the severity of CAAs. Patients with a maximal *Z* score >+2.5 are classified to have aneurysm, while between 2 and 2.5 is considered dilatation. CAAs can presents in the form of absence of tapering of coronary arteries, coronary artery ectasia, dilation and aneurysms. Other than CAAs these patients can have myocardial dysfunction (reduced ejection fraction, fractional shortening), valvular regurgitation, pericardial effusion and aortic root dilation [44]. It is recommended to perform frequent 2DE examinations during acute phase of KD. After discharge, 2DE should be done 2 weeks and then 4–6 weeks later. It should be noted that normal 2DE examination in first 7 days of illness does not exclude development of CAAs. More frequent 2DE assessment should be carried out in children with KD having >2 *Z* score coronary artery diameters [28].

4.11 Interpretation of 2DE Examination: A Word of Caution

1. Assessment of *Z* scores on 2DE is operator dependent and inter-individual variations are not uncommon. This can influence both acute and long-term management.
2. During the first 5–7 days of illness, CAAs are usually not seen. A normal 2DE during this period may be mistakenly interpreted as having excluded coronary involvement.
3. While normative data are available only for proximal segment of coronary arteries, there is paucity of literature on data for middle and distal segments of coronary arteries. Isolated involvement of distal segments of coronary arteries is uncommon but has been described [56].
4. It has been suggested that an aneurysm may be better defined as a dilatation that is 1.5 times or more than an adjacent segment. This circumvents the problems associated with *Z* scores.
5. Detailed and better evaluation of coronary arteries requires multiple transducer positions, imaging in multiple planes and high frequency transducers. Coronary artery diameters refer to the maximal internal luminal diameter. Measurements should not be taken at branching points.
6. Limitations of 2DE include difficulty in visualization of distal coronaries, frequent non-visualization of left circumflex coronary artery, difficulty in commenting on stenosis or thrombosis and limited field of vision in older children because of thick chest walls. Another problem is due to artifacts especially while scanning the right coronary artery or left circumflex coronary artery.
7. Several nomograms on *Z* scores are available and there may be variations in the measurements. Body surface area calculations have to be carried out meticulously and there is no consensus on the ideal method. It cannot be overemphasized that a trivial difference in measurement of weight and height (especially in infants and young children) can significantly impact the calculations of *Z* scores.
8. There are no normative data for "*Z*" scores for left circumflex coronary artery.

4.12 Coronary CT Angiography (CTCA)

Although 2DE has hitherto been considered the imaging modality of choice for coronary artery evaluation, CTCA is now increasingly being performed for better delineations of coronary arteries. CTCA is a useful modality for better characterization and delineation of coronary arteries dilatations, ectasia and aneurysms especially in the mid- and distal segments. It also provides precise details of aneurysm size, morphology, and thrombus. In the last decade, due to advancements in CT technology and the development of dual-source CT scanners (DSCT), it is now possible to obtain high resolution motion-free images at acceptable radiation dose. In the convalescent phase, CTCA can be used for delineation of complications such as intra-aneurysmal thrombus, segmental stenosis, and mural calcifications [57].

4.13 Management

4.13.1 Acute Management

Main aim of therapy in KD is halting of acute phase inflammation and arterial damage. Management includes use of IVIg, aspirin with or without anticoagulant therapy.

4.13.2 Intravenous Immunoglobulin (IVIg)

IVIg is the standard of care for the patients with KD. It should ideally be administered in first 10 days of illness. In the acute stage, IVIg (2 g/kg) is given over 10–12 h as a single infusion along with oral aspirin [3, 28]. If diagnosis is made after 10 days, IVIg should still be given if fever is persistent, inflammatory parameters are raised or if CAAs are present. Administration of IVIg during acute stage has reduced the rate of coronary artery complications to less than 5%. Approximately 1–3% patients with KD can have recurrences [58].

4.13.3 Aspirin and Anticoagulation Therapy

Aspirin has anti-inflammatory and antiplatelet activity depending on the dose being used. It remains an essential component of management in KD. However, effect of aspirin on development of CAAs is inconclusive. During the acute phase of illness, aspirin should be administered at high (50–100 mg/kg/day) or moderate (30–50 mg/kg/day) doses 6–8 hourly [59, 60]. Anti-inflammatory dose of aspirin is usually continued until 48–72 h after the patient becomes afebrile. After discontinuation of anti-inflammatory dose of aspirin, low-dose aspirin (3–5 mg/kg/day) is started and continued for 6–8 weeks. At this time if there are no CAAs on 2DE, aspirin can be discontinued. For children who develop CAAs, aspirin may need to be given indefinitely [28].

Complications related to CAAs during the acute phase of KD include thrombotic occlusion of a coronary artery aneurysm and rarely coronary artery rupture leading to sudden cardiac death. Coronary artery thrombosis in patients with KD is contributed by acute inflammation, high platelet counts, endothelial dysfunction and stasis of blood flow due to abnormal dilatation. In patients with CAAs assessment with 2DE is mandatory to monitor size of aneurysm and presence of thrombus. Patients with large coronary artery aneurysms are at high risk of myocardial infarction especially in the first year after illness. They continue to be at increased life-time risk of developing coronary artery events [28]. Risk stratification of coronary artery aneurysm should take into account both current and maximal *Z* score. Along with a *Z* score classification the shape, location, number of aneurysms and coronary artery wall abnormalities should also be considered for prognostication and risk stratification [61].

In patients with small aneurysms, low-dose aspirin is adequate for thromboprophylaxis. However, treating physicians can consider addition of another antiplatelet agent (e.g., clopidogrel) in patients with moderate size aneurysms. Patients having large or giant aneurysms are at very high risk for coronary artery complications including thrombosis and rupture. These patients should be treated with a combination of antiplatelet and therapeutic anticoagulation therapy. This includes low-dose aspirin along with either low-molecular-weight heparin (LMWH) or oral warfarin. LMWH should be given as 1 mg/kg/dose subcutaneously every 12 h. LMWH may be preferred to warfarin in acute phase because of added effects of anti-inflammatory and remodeling action. Transition from LMWH to oral warfarin may be considered in situations where the aneurysm has stopped progressing [28].

4.14 Resistant KD

Majority of patients will respond to first dose of IVIg with rapid defervescence of fever and improvement in general well-being. However, approximately 10–20% of patients with KD may go on to develop recrudescent or persistent fever. Children who have axillary temperature ≥38.0 °C at 36 h after completion of therapy are said to have resistant or refractory KD [28]. There are multiple factors that have been associated with development of IVIg resistance. These include severity of disease and host genetic factors (e.g., polymorphisms in the Fcγ receptors). Patients having refractory KD are at increased risk of developing CAAs. Various scoring systems have been developed in Japan to predict IVIg resistance, but the validity of these scores in other countries remains a contentious issue.

4.14.1 Treatment Options for Resistant KD

There are no clear guidelines on management of patients with refractory KD [62]. The AHA guidelines recommended use of a repeat dose of IVIg (2 g/kg) in these

patients. Alternatively, the guidelines emphasize the role of intravenous pulse methylprednisolone (30 mg/kg/day, three doses) with tapering oral prednisolone. Administration of tapering course of prednisolone for 2–3 weeks with second dose of IVIg (2 g/kg) may also be considered in the retreatment of refractory KD patients. Infliximab (TNF-α blocker), given as a single dose (5–10 mg/kg) intravenously, is also an important choice in treatment of refractory KD and appears to decrease the chances of developing CAAs [28]. Use of infliximab is associated with prompt reduction of fever. At our centre we prefer to use infliximab as second line therapy [63]. Cyclosporine may also be considered as an option in these circumstances. In highly refractory cases, plasma exchange, cytotoxic agents, or other biologicals have been used [28]. There are a few recent reports of successful use of the IL-1 receptor antagonist, anakinra, for the treatment of highly refractory KD [64].

4.15 Long-Term Management

Long-term follow-up and management of patients with KD is based on risk stratification. Children with large CAAs may need lifelong follow-up. Long-term management includes counselling about a healthy lifestyle with balanced diet and exercise to avoid obesity and hypertension. Because these patients have already developed a cardiac risk factor (even if there are no obvious CAAs during acute stage), a second risk factor like obesity, hyperlipidemia, or hypertension must be avoided [28]. Uses of statins have also been advocated in these situations. Patients having large and giant aneurysms should undergo frequent 2DE examinations for monitoring of size and associated complications. These patients may also require CTCA at periodic (every 3–5 years) intervals [56].

4.16 Consequences of KD in Adulthood

Children with missed and untreated KD can have significant clinical consequences later in life. Even though coronary arteries with remodeled aneurysms may become anatomically normal, they continue to remain functionally abnormal. An increasing number of young adults are presenting to cardiologists with myocardial ischemia and infarction—it is not often realized that these could well be late manifestations of KD that has been missed in childhood. These consequences of KD in adulthood are grossly under recognized [65]. There is very little awareness amongst adult cardiologists regarding cardiovascular sequelae of KD and their management. Clearly there is a need for an improved evidence base to guide the care and management of adults with coronary artery damage following KD in childhood. Whenever a young adult is presenting with myocardial ischemia and there is marked ectasia or proximal coronary artery involvement, possibility of untreated KD in past should be entertained [66].

4.17 AHA 2017 Guidelines: The Debate Continues

The AHA has published an update on criteria for diagnosis of KD in 2017. While the presence of fever remains an essential criterion and there is no change in the five principal clinical manifestations of the disease, the scientific committee has suggested several amendments. The new guidelines emphasize that some clinical features of KD may subside by the time the patient reaches a clinician. In such situations the clinical findings that have disappeared can also be taken into account for fulfilment of criteria. Similarly, the issue of diagnosis in young infants has been addressed at length. The guidelines mention that any infant with unexplained fever lasting for a week or more should be evaluated for underlying KD. This cannot be overemphasized.

In the 2017 guidelines, the terms *incomplete KD and atypical KD* have been used interchangeably. However, these are distinct clinical entities and this fact needs to be kept in mind while evaluating a patient. Desquamating groin rash has been included as one of the other clinical findings. It is known that erythema or desquamation of perineal/perianal region occurs earlier than classic periungual peeling and thus may facilitate early consideration of the diagnosis.

The AHA 2017 guidelines emphasize on the use of *Z* score for assessment of coronary artery size. However, the difficulties involved in calculation of an accurate '*Z*' score that is reproducible across centres have not been detailed at length.

4.18 Difference Between Japanese Ministry of Health and AHA Guidelines [28, 29, 54]

1. In the Japanese criteria fever is not taken as an essential prerequisite for diagnosis. In other words, a diagnosis of KD can be offered even in absence of fever while using the Japanese criteria.
2. Definition of coronary artery lesion in Japanese Ministry of Health guidelines is based on absolute dimensions, while AHA 2017 guidelines have classified the CAAs on basis of "*Z*" scores (Table 4.4).
3. Refractory KD has been defined as persistence of fever more than 36 h despite treatment as per AHA guidelines. However, the cut-off for duration of fever is 24 h in Japanese guidelines.

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Systemic-Onset Juvenile Idiopathic Arthritis

5

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5.1 Introduction

Systemic juvenile idiopathic arthritis (SJIA) is a rare disease of unknown etiology characterized by arthritis and systemic symptoms such as highly spiking daily fever, evanescent skin rash, organomegaly, and serositis. Evidence shows that SJIA is probably not a single disease but a diverse group of clinically and genetically distinct illnesses [1]. It is classified both as one of the Juvenile idiopathic arthritis (JIA) categories and also among the autoinflammatory diseases. Abnormalities in the innate immunity components, dramatic response to IL-1 inhibitors, occurrence at very young age and absence of pathogenic autoantibodies has led many researchers to consider SJIA as a complex, polygenic autoinflammatory disorder [2–5].

SJIA is probably the most severe forms of JIA, causing considerable morbidity and mortality due to several complications that may occur along the disease course. The macrophage activation syndrome (MAS), a form of secondary hemophagocytic lymphohistiocytosis (HLH), often appears in SJIA individuals and it still carries significant mortality despite increased awareness and novel therapies.

5.2 Classification

Systemic juvenile idiopathic arthritis (SJIA) is one of the juvenile idiopathic arthritis (JIA) categories according to the International League of Associations for Rheumatology (ILAR) classification criteria [6]. Classification of SJIA requires the presence of arthritis and a documented quotidian fever of at least 2 weeks duration, plus one of the following: typical rash, generalized lymphadenopathy, enlargement

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of liver or spleen, or serositis. Children with SJIA may have a delayed diagnosis, particularly in the "pre-arthritic" phase, when the systemic disease is already prominent. At this stage, ILAR criteria are not sensitive enough and do not allow the inclusion of such patients. Individuals with the same signs and symptoms (probably the same disease) who present their disease onset after the 16th birthday are diagnosed with adult-onset Still's disease (AOSD) and could be classified using different criteria set, such as the Yamaguchi's criteria [7], which is probably the most widely used set of criteria for AOSD. Five or more criteria are required, of which two or more must be major. Major criteria are the following: (1) fever >39 °C, lasting 1 week or longer, (2) arthralgia or arthritis, lasting 2 weeks or longer, (3) typical rash, and (4) leukocytosis >10,000/mm^3 with >80% polymorphonuclear cells. Minor criteria are the following: (1) sore throat, (2) recent development of significant lymphadenopathy, (3) hepatomegaly or splenomegaly, (4) abnormal liver function tests, (5) negative tests for antinuclear antibody (immunofluorescence), and (6) negative rheumatoid factor (IgM). Exclusion criteria are the following: infections, malignancies (mainly malignant lymphoma), and other rheumatic diseases (mainly systemic vasculitides). Small cohorts of patients with SJIA have revealed that Yamaguchi criteria seem to be more efficacious in the absence of arthritis. However, these criteria have not been formally validated in children [7, 8].

The SJIA spectrum includes those patients with benign, monocyclic course and those with protracted, severe forms, which lead to joint destruction. In the future, more precise classification based on genetic variants and gene expression may not only identify homogeneous groups but also direct towards personalized treatment [9, 10].

5.3 Epidemiology

According to different studies in different parts of the world, the prevalence of SJIA is approximately 3.5/100,000 children, while incidence ranges between 0.4 and 0.9 per 100,000 per year [11, 12]. A large number of studies have demonstrated equal distribution between girls and boys [13, 14]. Age at onset is virtually any age before the 16th birthday; however, the peak incidence has been registered at 6 years [15]. SJIA represents nearly 5–25% of patients with JIA in cohort studies, but this proportion differs in different parts of the world [12–16]. Despite being one of its most rare subtypes, SJIA accounts for nearly two-thirds of the total mortality rate in JIA [12–16]. Recently, Davies et al. showed that mortality rate for SJIA patients is 3.9/1000 person-years compared with 0.6/1000 person-years in non-systemic JIA patients, being the standardized mortality rate was highest in SJIA (8.3 with 95% CI 2.7–19.4) [17].

5.4 Pathogenesis

The pathogenic mechanisms of SJIA are poorly understood. Growing evidence aims at a major dysbalance in innate immunity pathways: disturbed pro-inflammatory cytokine expression patterns and inappropriate down-regulation of immune

activation are major determinants of the immunological abnormalities in SJIA [3]. There is ample evidence supporting the autoinflammatory nature of SJIA, at least in its early phases. Expansion and dysfunction of circulating innate immune effector cells—neutrophils, monocytes, and natural killer (NK) cells—and increased expression of pro-inflammatory molecules and receptors, as well as lower expression of regulatory mediators, have been reported and proposed as key pathogenic mechanisms of the disease [18, 19]. Some authors hypothesize that SJIA could evolve in a biphasic fashion, from a predominantly autoinflammatory disease in its early stages into one in which interleukin (IL)-17 mediated autoimmunity may have a role in joint-related outcomes [20–22].

Several studies support the predominant pathogenic role of IL-1β, IL-6, and IL-18 in SJIA. Dysbalance of IL-10, IL-17, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α may also be involved [23–25]. Shimizu et al. supported the heterogeneity of the disease by describing different plasma cytokine profiles in patients with SJIA: an IL-6-dominant group (with predominant arthritic symptoms and good response to IL-6 inhibitors) and an IL-1β/IL-18-dominant group (with mainly systemic symptoms, predisposition to develop MAS, and good response to IL-1 blockers) [26, 27].

There is substantial evidence that IL-1β plays a major role in SJIA. Pascual et al. showed not only high levels of IL-1β in supernatants of stimulated peripheral blood mononuclear cells (PBMCs) of SJIA patients but also demonstrated that serum of SJIA patients induced transcription and secretion of IL-1β by healthy PBMCs [23]. However, other researchers could not observe the same phenomena [28, 29]. Gene expression profiling in PBMCs demonstrates up-regulation of components of the IL-1, IL-18 and toll-like receptor (TLR) signaling pathways and of components of the NLRP3 inflammasome [23, 30, 31]. Moreover, the clinically demonstrated dramatic response to IL-1 blocking agents also supports the pathogenic role of IL-1 in SJIA [23, 32]. IL-18 may also have a disease-promoting role in SJIA. Excessive IL-18 plasma levels reflect disease activity and they may persist even during inactive disease phases [24, 25, 28, 33, 34]. Elevated IL-6 levels have been demonstrated in synovial fluid as well as in plasma of SJIA patients in several studies. Their levels correlated with disease activity, systemic symptoms, and inflammation-related laboratory abnormalities (anemia and thrombocytosis) [35–38]. Also, IL-6 inhibition through the use of anti-IL-6 receptor-monoclonal antibodies has proven highly efficacious in controlling systemic and arthritic symptoms in SJIA, thus supporting the pathogenic role of IL-6 [38]. Additionally, in vitro evidence demonstrates a reduced inhibition of IL-6 by IL-10 in patients with SJIA compared to healthy controls [39, 40]. Animal models of SJIA also endorse the pathogenic role of IL-1β, IL-6, and IL-18 [41–44]. On the other hand, IFN-γ levels are not particularly elevated during active phases of SJIA, but this cytokine seems to be central in the development of MAS [45].

NK cell number and function are abnormal at least in a proportion of patients with SJIA. Some investigators have found decreased numbers of NK cell in whole-blood samples of SJIA patients as compared to patients with other categories of JIA or healthy controls [46–49]. Grom et al. demonstrated reduced perforin expression

and suppressed cytolytic activity of NK cells in a number of SJIA patients [48]; the same group also showed that a proportion of patients with SJIA who have not yet had an episode of MAS exhibit decreased NK cytolytic function and absence of circulating $CD56^{bright}$ population [49]. Wulffraat et al. found that these abnormalities were reversible upon autologous stem cell transplantation [50]. Put et al. [51] could not replicate these findings but demonstrated decreased interleukin IL-18-induced IFN-γ production and granzyme K expression in $CD56^{bright}$ NK cells. These authors also found increased expression of inflammatory pathways, increased expression of TLR4 and S100A9, and decreased expression of immune regulatory genes such as granzyme K and IL-10 receptor [52]. It has been proposed that the characteristic inflammatory *milieu* of SJIA (rich in IL-6 and IL-18) alters NK cell function and numbers, leading to decreased production of IFN-γ, perforin, and granzyme K, and to the simultaneous increased production of proinflammatory cytokines [52, 53]. de Jager et al. found that the decreased NK cell responses to IL-18 are associated with decreased phosphorylation of the IL-18 receptor [54].

Monocytes seem to be a key effector cell in the pathogenesis of SJIA. Expansion and activation of monocytes in active SJIA, likely related to increased monocyte resistance to apoptosis, have been clearly demonstrated by Macaubas et al. [55]. Monocytes from SJIA patients appear to have a mixed polarization phenotype, with features of both classically (M1) and alternatively (M2) activated populations [56]. Activated macrophages with an M1 phenotype are potential sources of pro-inflammatory cytokines and those with an M2 phenotype would be responsible for a compensatory, regulatory mechanism during inactive state. The same authors showed impaired IFN/STAT1 signaling in monocytes from SJIA patients, which suggested a skewing toward a regulatory M2 phenotype [57]. Schulert et al. demonstrated that the microRNA, miR-125a-5p (whose expression on monocytes is elevated in patients with active disease) drives monocytes polarization to a regulatory phenotype [58]. Additionally, under-expression of the IL-1 inhibitor, aryl hydrocarbon receptor (AHR) may skew monocytes toward macrophage differentiation [59].

The predominant role of the innate immune system in the pathogenesis of SJIA is also demonstrated by the uniquely high serum concentrations of products of activated granulocytes and monocytes, the proteins S100A8 (or myeloid-related protein [MRP]8), S100A9 (or MRP14) and the neutrophil-derived S100A12, which may act as endogenous TLR ligands [60–62].

Genetic studies in SJIA are scarce due to the low frequency of the disease and usually performed on underpowered samples (Table 5.1). Polymorphisms in genes of different innate immunity proteins involved in the amplification or control of the inflammatory response have been associated with the disease. A large genome-wide association study of SJIA has shown an association with the HLA class II locus, consistent with T-cell-mediated autoimmunity. This study involved 988 SJIA patients from different countries and it identified several SJIA-associated risk loci: the MHC locus on chromosome 6 (HLA-DRB1*11 was strongly associated with SJIA) and another susceptibility locus on the short arm of chromosome 1 (1p36.32) [63]. Another study on a smaller sample supported the HLA-DRB1*11 association [64]. On the other hand, polymorphisms in non-HLA genes such as TNF, IL-1, IL-6,

Table 5.1 Genetic association studies in SJIA

Gene/region	Polymorphism/sequence variation/position	MAS	Ref
IL-1	rs6712572, rs2071374, rs1688075	No	65
IL-1R	rs12712122	No	65
IL-6	rs1800795	No	67
MIF	rs755622	No	69
IL-10	rs1800896	No	71
IL-20	rs1400986	No	71
MUNC 13-4	12 SNPs, 2 mutations	Yes	80
	rs35037984	Yes	81
PRF1	–499 C > T, Ala91Val	Yes	79
IRF5	rs2004640	Yes	73
STXBP2	rs151257815, fs7705108	Yes	81
LYST	rs147794568, rs115330112	Yes	81
SLC26A2	rs1541915, rs245056, rs245055, rs245051, rs245076, rs8073	No	77
*HLA-DRB1*11*	rs115124338	No	63
	position 32660042		64
HLA-DRA#	rs41291794	No	63
LOC284661, AJAP1#	rs72632736	No	63

#Closest genes in Genome-wide association studies

macrophage inhibitory factor (MIF), interferon regulatory factor (IRF) 1 and IL-10 have been reported to be associated with the disease [65–72]. Similarly, polymorphisms in IRF5 have been associated with susceptibility to MAS [73]. Additional genetic abnormalities affecting other components of the innate immune system, such as *P2X7* (encoding an ATP receptor involved in IL-1 regulation), have also been reported [29].

Polymorphisms in genes responsible for well-known monogenic autoinflammatory disorders, such as the *MEFV* gene, and duplications in the *NLRP* gene cluster have been reported in patients with SJIA [74–76]. Additionally, an association between susceptibility to SJIA with polymorphisms within *SLC26A2*, a gene related to diastrophic dysplasia, has been reported [77]. The implications of such associations on the phenotypic expression of SJIA are still unknown. Several polymorphisms of unknown significance and protein-altering variants in genes coding for proteins involved in the cytolytic pathway have been described in patients with SJIA. Variants in *PRF1*, *LYST*, *MUNC13-4*, and *STXBP2* genes may be related to susceptibility to develop MAS and demonstrate the genetic overlap (albeit partial) between SJIA and HLH [19, 78–81].

A monogenic, autosomal-recessive form of SJIA has been described in six consanguineous families from southern Saudi Arabia and Lebanon. A missense mutation in the gene *FAMIN* (Fatty Acid Metabolism-Immunity Nexus, formerly also referred to as *LACC1*) was found by whole-exome sequencing and confirmed by Sanger sequencing in patients with an SJIA-like disease that satisfied ILAR classification criteria [82, 83].

5.5 Diagnosis: Differential Diagnosis

There is no gold standard for the diagnosis SJIA, and therefore, it is made on the basis of a combination of clinical features and the exclusion of confounding conditions [13]. There are no specific biomarkers that allow the differentiation of the disease from other conditions or JIA categories [84].

The spectrum of clinical manifestations is wide and may overlap with those that are common in other causes of the febrile syndrome in childhood. These include infections such as bacterial endocarditis, cat scratch disease, Lyme disease, Brucellosis, viral infections, Mycoplasma infections; inflammatory diseases including acute rheumatic fever, Kawasaki disease (KD), sarcoidosis, Systemic Lupus Erythematosus, systemic vasculitis; and autoinflammatory diseases (Familial Mediterranean Fever, Mevalonate Kinase Deficiency, TNF Receptor-Associated Periodic Syndrome, and Cryopyrin-Associated Autoinflammatory Syndromes, which include the Muckle-Wells syndrome, Familial Cold Autoinflammatory Syndrome, and Chronic Infantile Neurological, Cutaneous, and Articular Syndrome) [85].

Children with SJIA may fulfill criteria for KD at presentation. It has been estimated that 0.2% of patients with a diagnosis of KD will later be diagnosed as SJIA. Features suggestive of SJIA are Caucasian ethnicity, MAS, an incomplete KD phenotype, and persistence of arthritis [86].

5.6 Clinical Manifestations

The typical clinical features of SJIA are a combination of arthritis and systemic symptoms, such as fever, rash, lymphadenopathy, serositis, and hepato-splenomegaly. Patients with SJIA starting before age 18 months show more systemic inflammatory features than children with later disease onset [15].

Fever is present in virtually all patients [13]. In many cases, it may precede the onset of arthritis by weeks or months. The fever pattern is typically quotidian and it occurs once or twice daily, more often during the evening, commonly reaching 39 °C [6]. Temperature exceeding 40.5 °C is extremely rare. Fever is coincident with the rash in 80% of patients. While the child is febrile, other symptoms such as arthritis, rash or serositis may worsen and significantly disturb activities of daily life [87]. The classic fever pattern is not present in all patients; morning (12%), bi-daily (15%), intermittent (27%), and unremitting (5%) fever patterns are also observed [13].

Arthritis is present at onset in 88% of patients, and it may appear months or years after disease onset [12, 88]. The most frequently involved joints at presentation are wrists, knees, ankles, cervical spine, and hips. The joint pattern is usually symmetrical, polyarticular (45%) or oligoarticular (40%), while the involvement of a single joint is rare [12, 13]. Synovial cysts are frequent, especially in upper limbs [89]. They may resolve spontaneously, but occasionally cyst rupture may cause diffuse swelling and mimic thrombophlebitis [90]. At least 40% of patients will show a chronically active arthritic course, and bilateral, destructive changes in hips and wrists may occur [90].

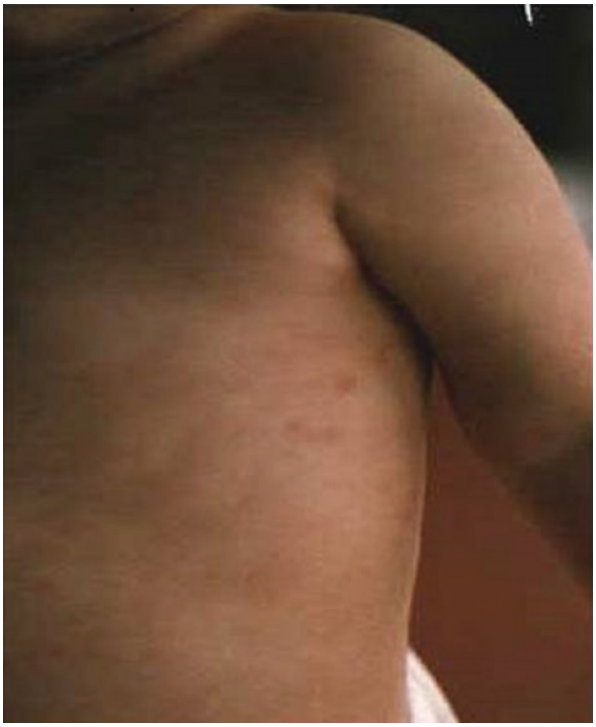

Fig. 5.1 Erythematous, salmon-pink colored, rash in a patient with active Systemic juvenile idiopathic arthritis

Nearly 80% of patients exhibit skin rash at onset and during disease activity phases [13, 91]. It is morbilliform, evanescent (vanishes within a few minutes to a few hours), and it correlates with the acute febrile episodes. Macular papules are usually salmon pink-colored or erythematous, surrounded by a pallor zone; purpuric lesions are not seen and pruritus may accompany in 5% of cases [12, 91]. The diameter of the individual lesions usually ranges between 2 and 5 mm, although larger, coalescent lesions may occur [12]. Sites where rash is most common are trunk and proximal extremities. Koebner phenomenon (emergence of linear distribution of lesions next to the site of injury) can occur [87, 92] (Fig. 5.1).

Pathology usually demonstrates subdermal, perivascular rich infiltrates of neutrophils and monocytes, accompanied by a marked expression of endothelial adhesion molecules. Keratinocytes are activated and express MRP8 and MRP14 [91].

Generalized lymphadenopathy is observed in 25–30% of patients [11, 13, 93]. It usually consists of mobile, rubbery nodes on the cervical, axillary, inguinal, epitrochlear, mesenteric, and mediastinal groups. They may mimic malignances like lymphomas, often leading to biopsies; pathology usually reveals reactive changes [12, 87, 94]. Lymphedema (associated with inflammation of the lymphatic vessels) is a rare manifestation [95].

Hepatomegaly is frequent but does not occur as often as splenomegaly, which has been described in 50% of patients and is usually evident during active phases. Enlargement of the liver is usually moderate and associated with only mild abnormalities of liver enzymes. However, massive hepatomegaly may occur and cause abdominal distention and pain [12]. Liver biopsy usually exhibits periportal inflammatory infiltrates. Hepatosplenomegaly may be the initial sign of amyloidosis [90].

Pericarditis is the most common form of serositis and it can be detected in nearly 10–15% of patients. It is more common in older patients and may precede the onset of arthritis. It is usually benign and resolves with no sequelae. On the other hand, the rare myocarditis has a poorer prognosis. Most pericardial effusions are asymptomatic, although some children exhibit dyspnea or precordial pain [96]. On the other hand, pleuritis and peritonitis are rare [12].

Less frequent manifestations are the following: aseptic meningitis, pseudotumor cerebri, seizures, encephalopathy and cerebral hemorrhage (as part of MAS), myocarditis, endocarditis, congestive heart failure, coronary artery dilatation, pulmonary artery hypertension, interstitial lung disease, lipoid pneumonia, orbital tenosynovitis (Brown's Syndrome), uveitis, glomerulonephritis, and nasal septal perforation [97–101].

5.7 Laboratory and Biomarkers

Laboratory findings reflect systemic inflammation during active phases. There are no specific tests but typically high C-reactive protein and erythrocyte sedimentation rate (ESR), leukocytosis with neutrophilia, marked thrombocytosis, and microcytic anemia are present during active phases. Limenis et al. reported the laboratory variables voted for in a consensus process aimed at the validation of a tool for assessment of disease activity in SJIA [102]. ESR, CRP, hemoglobin, platelet count, ferritin, albumin, white blood cell count, neutrophil count, D-dimer, alanine transaminase, and aspartate transaminase were considered to be of value by the authors. Autoantibodies are absent and complement levels may be normal or elevated. ANA titers might increase over time in a proportion of patients with SJIA. It is unclear if this is of pathogenic relevance or an epiphenomenon [103]. The role of ACPA anticitrullinated protein antibodies) in SJIA has not been defined yet [103, 104]. ACPA has been related to polyarticular and oligoarticular JIA, particularly rheumatoid factor-positive polyarticular JIA. Different studies have demonstrated low levels of ACPA in a small percentage of SJIA patients [105]. Despite the predictive role of ACPA in the development of erosions in patients with rheumatoid arthritis, they have no predictive value for bone erosions in SJIA [105, 106].

Serum biomarkers that reflect disease activity include ferritin, S100A8, S100A9 (or the S100A8/S100A9 complex, calprotectin), and S100A12. The serum levels of these proteins are significantly higher in patients with SJIA than in patients with confounding conditions (such as Kawasaki disease or infections) and correlate well with disease activity and response to treatment, which has led some investigators to propose them as predictors of relapses [61, 85, 107–110].

A large study identified several biomarkers of diagnostic or prognostic value in SJIA [84] (Table 5.2). Most of these proteins are secreted by activated granulocytes, monocytes, and immature macrophages, and their serum levels are significantly higher in patients with SJIA than in patients with confounding conditions. Additionally, they correlate well with disease activity and response to treatment, and they have a role in the prediction of relapses [85]. Particularly S100A8/A9 has been shown to be a sensitive biomarker for subclinical disease activity and also a predictor of relapses in SJIA [111]. Additionally, some investigators propose that serum levels of IL-18 and IL-6 might define subsets of SJIA [112].

Plasma and urine proteomic profiling may exhibit a "signature" associated with the active phases of the disease [107, 113]. One study demonstrated that

Table 5.2 Laboratory tests and biomarkers (BM) in SJIA and MAS

	SJIA (active phase)	MAS	Clinical value
Routine laboratory and BM			
C-reactive protein	↑	N/↑↑	Predictive for flare. Distinguishes active from inactive disease.
Erythrocyte sedimentation rate	↑	N/↑/↓	Predictive for flare. Distinguishes active from inactive disease. Discriminating MAS from active SJIA.
White blood cells	↑	N/↑/↓	Predictive for flare. Distinguishes active from inactive disease. Discriminating MAS from active SJIA.
Neutrophil count	N/↑	N/↓	Predictive for flare. Distinguishes active from inactive disease. Discriminating MAS from active SJIA.
Hemoglobin	↓	↓	Distinguishes active from inactive disease.
Platelet count	N/↑	N/↓	Predictive for flare. Distinguishes active from inactive disease. Discriminating MAS from active SJIA.
Triglycerides	N/↑	N/↑↑↑	Discriminating MAS from active SJIA.
Na	N	N/↓	Discriminating MAS from active SJIA.
Albumin	N/↓	↓	Distinguishes active from inactive disease.
Lactate dehydrogenase	N/↑	N/↑↑↑	Distinguishes active from inactive disease. Discriminating MAS from active SJIA.
D-dimer	N/↑	N/↑↑	Distinguishes active from inactive disease. Discriminating MAS from active SJIA.
Alanine transaminase	N/↑	N/↑↑↑	Distinguishes active from inactive disease. Discriminating MAS from active SJIA.
Aspartate transaminase	N/↑	N/↑↑↑	Distinguishes active from inactive disease. Discriminating MAS from active SJIA.
Ferritin	↑	↑↑↑↑	Distinguishes active from inactive disease. Discriminating MAS from active SJIA.
Fibrinogen	N/↑	N/↓↓	Distinguishes active from inactive disease. Discriminating MAS from active SJIA.

(continued)

Table 5.2 (continued)

	SJIA (active phase)	MAS	Clinical value
Non-routine laboratory and BM			
SAA (serum amyloid A)	↑	↑	Predictive for flare. Distinguishes active from inactive disease.
S100A8/S100A9	↑	↑	Discrimination of active vs. inactive disease.
S100A12	↑	↑	Distinguishes active from inactive disease.
sCD163 (hemoglobin scavenging receptor)	↑	↑↑↑	Discriminating MAS from active SJIA.
sCD25 (soluble IL-2 receptor alpha)	↑	↑↑↑	Discriminating MAS from active SJIA.
Neopterin	N/↑	↑↑↑	Discriminating MAS from active SJIA.
COMP (cartilage oligomeric matrix protein)	↑	?	BM in SJIA vs. other non-arthritis conditions.
FSTL-1 (follistatin-like protein 1)	↑	?	BM in SJIA vs. other non-arthritis conditions.
OPG (osteoprotegerin)	↑	?	BM in SJIA vs. other non-arthritis conditions
sST2 (soluble ST2 or IL-1 receptor-like)	↑	?	BM in SJIA vs. other non-arthritis conditions
TTR (transthyretin)	↑	?	BM in sJIA vs. other non-arthritis conditions. Predictive flare?

programmed death ligand-1 (PD-L1) expression on monocytes is significantly lower in SJIA than in patients with other febrile illnesses (KD, infections) [110]. Gene expression analysis may discriminate between active and inactive phases and provide additional predictors of flares or MAS [19]. A "multimarker approach" has recently been used to predict the risk of disease activity in pediatric lupus predicting nephritis [114]. A biomarker panel might be cost-effective in identifying different subgroups in SJIA, predict flares, and potentially preclude MAS.

5.8 Imaging

Radiographic changes are not specific, although hip joint abnormalities, juxta-articular osteoporosis, and epiphyseal irregularities are more common in SJIA than in other forms of JIA [115]. Early changes include soft tissue involvement and juxta-articular osteoporosis. Abnormalities in the development and maturation of ossification centers, joint space narrowing due to cartilage damage, bony erosions, and growth abnormalities usually appear later during the disease course. Joint

damage is more frequent in hips, wrists, temporomandibular joints, and cervical spine [15, 116]. A significant proportion of SJIA patients develop joint damage within 2 years while 75% of patients show radiographic damage at 5 years after diagnosis [117, 118]. Particularly in hips, rapid progression can be observed despite aggressive treatment [119].

5.9 Complications

Growth delay is associated with active disease, corticosteroids treatment, and poor nutrition. Growth delay was reported to be present in 18% of children 5 years after disease onset [120]. Catch-up growth is incomplete in 30% of patients and the mean final height is −2 SD [15, 121, 122].

Amyloidosis is a rare complication. The incidence of amyloidosis is between 1% and 10%, but it may vary according to the country where the patient lives. SJIA patients from Turkey evidence a higher incidence [123]. It typically occurs in patients with persistently active disease and elevated levels of serum amyloid-A (SAA) and other inflammatory proteins. It is a late complication, usually developing after several years after disease onset: it may develop as early as 1 year or as late as 23 years after onset. The diagnosis is made with a biopsy (the rectal submucosa is one of the preferred sites for obtaining a specimen) [75, 124]. Lately, the use of efficacious biologic agents has led to better control of clinical and biochemical signs of inflammation, and consequently to a dramatic decrease in the frequency of this complication [125].

Longer disease duration, persistent inflammatory activity, use of corticosteroids, biologic action of proinflammatory cytokines, muscle atrophy, and sedentarism predispose SJIA patients to osteoporosis. Vertebral fractures are frequent, while bone mineral density catch-up is usually incomplete [126–129].

5.10 Macrophage Activation Syndrome

MAS, a form of secondary or reactive HLH, is a serious complication of SJIA and it is associated with a mortality rate approaching 10–20% [130, 131]. It is caused by an exaggerated and uncontrolled activation and expansion of T cells and macrophages, which are the sources of massive amounts of proinflammatory cytokines leading to a multiorgan, hyperinflammatory state [132]. Although it may occur in the context of different rheumatic conditions, SJIA is by far the most common cause of MAS [133]. Even though it may develop during active SJIA in the absence of a recognizable trigger, different factors such as infections (remarkably EBV-related) or changes in therapy have been associated with its onset [131, 134, 135]. The syndrome occurs in 5–20% of SJIA patients, but this proportion may reach 50% if cases of subclinical MAS are included [96]. MAS represents the most severe end of a continuous clinical spectrum of disease activity in SJIA. The syndrome may develop either abruptly or progressively over the course of several days; clinical suspicion

and timely diagnosis should occur before the full-blown picture is overt and chances of organ failure increase. Increased transaminase levels, abnormal coagulation screen, a fall in fibrinogen and platelet count, and increasing serum ferritin (presumably originating from activated macrophages) levels may precede the onset of MAS [136]. Serum levels of soluble CD163 and sCD25 (or Interleukin-2 Receptor α-Chain), which are markers of activation and expansion of macrophages and T cells, respectively, may help in the diagnosis of MAS and assessment of treatment response [137]. Typical features are continuous fever (as opposed to the intermittent fever occurring during active SJIA), fixed rash that may include petechiae or purpura, encephalopathy, hepatosplenomegaly, and a paradoxical improvement in the joint symptoms. Laboratory abnormalities include pancytopenia (or decreasing white blood cell and platelet counts), elevated liver enzymes, coagulopathy, hyperferritinemia, hypertriglyceridemia, normal or falling ESR, hypofibrinogenemia, elevated D-dimers, reduced NK-cell numbers and cytotoxic activity, and increased serum sCD25 levels [131, 136]. A recent study showed that serum Angiopoietins 2/1 (regulators of endothelial cell function) ratio was significantly elevated during MAS as compared to the ratio observed during the active and inactive phases of SJIA, indicating disruption or activation of the endothelial cells [137].

In 2005, Ravelli et al. published a set of clinical and laboratory diagnostic criteria which have been useful in the clinical recognition of the syndrome [138]. Recently, the classification criteria for SJIA-associated MAS were developed by an international panel of experts [139]. These criteria may be less sensitive for classifying MAS in SJIA patients who develop MAS while treated with biological agents such as IL-1 or IL-6 inhibitors [140]. Evidence of hemophagocytosis is commonly found in bone marrow aspirates but it is not a mandatory criterion for diagnosis [138]. Clinical features and course of MAS are comparable between patients irrespective of their evidence of hemophagocytosis [141].

5.11 Treatment

The optimal management of SJIA requires a multidisciplinary team that includes pediatric rheumatologists, nurses, physiotherapists, occupational therapists, social workers, and psychologists. The initial pharmacological therapy consists of nonsteroidal anti-inflammatory drugs supplemented with corticosteroids in variable amounts according to the severity of the disease [142], but the more ample availability of anti-IL-1 agents has led some groups to use anakinra (ANK) very early during the disease course, even before or instead of the prescription of corticosteroids [143–146]. Indications for the use of steroids are the presence of anemia, myocarditis, pericarditis, pleuritis, peritonitis, and MAS. Recommendations for steroid dosing and tapering have been developed [147]. Pulse methylprednisolone (10–30 mg/kg/dose, up to 1 g/daily, for 3 consecutive days) may be useful in certain circumstances, such as MAS.

Traditional disease-modifying agents have not demonstrated consistent efficacy in SJIA. Methotrexate may be effective in patients with no systemic features,

Table 5.3 Controlled clinical trials assessing the efficacy of different biologic agents in SJIA. Only the results of the double-blind phase are shown

Agent	Sample	Primary endpoint	Efficacy (%)	Reference
Tocilizumab	56 patients	ACR Pedi 30 + CRP < 15 mg/L	91	[38]
	112 patients	ACR Pedi 30 + resolution of fever + taper of steroids	85	[176]
Anakinra	24 patients	ACR Pedi 30 + resolution of systemic symptoms + 50% drop in CRP/ESR; CRP < 15 mg/L	75	[167]
Canakinumab	84 patients	ACR Pedi 30 + resolution of fever	84	[32]
	100 patients	Absence of flare	74	
Rilonacept	68 patients	ACR Pedi 30 + resolution of fever + taper of steroids	57	[175]
	24 patients	ACR Pedi 30 + resolution of systemic symptoms	35.3	[174]

ESR erythrocyte sedimentation rate, *CRP* C-reactive protein

although it is not as effective as in other forms of JIA [148]. Thalidomide and atorvastatin have been modestly effective in small series or single, refractory cases [149, 150]. On the other hand, data on the efficacy of high-dose intravenous immunoglobulin (IVIG) are conflicting [151, 152].

The advent of biologic medications has provided unprecedented efficacious agents for the treatment of SJIA, dramatically changing the outcome of patients (Table 5.3). The first biologic agents that were approved for the treatment of JIA (etanercept and adalimumab) have been used for the treatment of SJIA with conflicting results. SJIA patients with systemic features were excluded from the pivotal clinical trials of anti-TNF agents and abatacept in JIA [153–155] and they have usually failed to show sustained efficacy in children with SJIA in routine clinical practice, especially in patients with active systemic features [156–161]. However, these agents might be useful in patients without systemic features or during the late, predominantly arthritic phases of the disease [162].

Several observational studies and clinical trials have shown the efficacy and safety of ANK in the treatment of SJIA, at least in the first year of therapy [23, 163–168]. Most studies have demonstrated that ANK is effective in suppressing systemic signs more than joint inflammation. Gattorno et al. showed that SJIA patients can be divided into two different groups according to their response to ANK: good responders (about 40% of treated patients) and incomplete or non-responders [29]. In a French multicenter, randomized, double-blind, placebo-controlled trial, ANK demonstrated rapid efficacy in 8 of 12 SJIA refractory patients during the double-blind phase of the trial, while 7 out of 16 patients reached 30% improvement in a composite score (ACR 30) during the12-month long, open-label, extension phase [167, 169]. Interestingly, one patient was diagnosed with Crohn's disease after receiving ANK during the trial [167]. Observational, non-controlled, retrospective and prospective studies have shown that ANK (both in combination with steroids and DMARDs or alone) is effective as first-line therapy, it is associated with rapid resolution of systemic symptoms and could probably alter the course

of SJIA [143, 144, 146]. Interestingly, treatment with ANK has been demonstrated to induce normalization of soluble inflammatory markers as well as gene expression abnormalities [30, 143, 167]. Besides, ANK has shown efficacy in the treatment of SJIA-associated MAS [170]. Toxicity has been reported in several cases: infections, severe skin reaction at the injection site, and hepatitis (or subtle MAS) have occurred in several patients [165, 171].

Canakinumab (CNK), an anti-IL-1β monoclonal antibody, was rapidly effective in a preliminary, phase II, multicenter, open-label, dose-escalation study involving 24 children [172]. CNK was more effective in children with fewer swollen joints. A larger phase III trial including 177 SJIA patients with active systemic symptoms demonstrated its rapid efficacy in the vast majority of treated children, allowing dose reduction or discontinuation of corticosteroids [32]. After 15 days of treatment, ACR30 was achieved by 84% of patients on CNK, and inactive disease state was observed in 33%. At the end of the withdrawal phase, 62% of CNK-treated patients and 34% of patients in the placebo group had inactive disease. The drug was generally well tolerated but MAS occurred in seven patients. Additionally, CNK therapy proved to induce down-regulation of innate immune response genes in SJIA patients [173].

Rilonacept (RLN), an anti-IL-1 soluble decoy receptor protein, was tested in a controlled clinical trial where no significant differences in efficacy between the RLN- and the placebo-treated patients were observed in the double-blind phase, but fever and rash subsided during the open-label phase [174]. Another trial involving 71 SJIA patients with long-standing disease and paucity of systemic features demonstrated that shorter time to response occurred in the RLN arm as compared to the placebo arm. Liver enzymes elevation and MAS were among the reported severe adverse events [175].

Tocilizumab (TCZ), a humanized anti-IL-6 receptor monoclonal antibody, showed marked efficacy and safety in a double-blind, placebo-controlled, withdrawal, phase III trial enrolling 56 patients [38]. ACR 30, 50, and 70 responses were achieved by 91%, 86%, and 68% of patients, respectively, at the end of the open-label phase of the study. These results were confirmed in a larger trial involving 112 patients [176]. Of interest, TCZ allowed improved growth and normalization of insulin-like growth factor 1 (IGF-1) in the majority of these patients [177]. One surveillance study on TCZ performed in Japan demonstrated a more frequent occurrence of MAS and serious infusion-related adverse in routine clinical practice than in clinical trials [178].

Clinical experience in the real world (outside clinical trials) with biologic agents has also demonstrated their efficacy in SJIA, especially for IL-1 and IL-6 inhibitors. A recent paper reporting the German registry data on biologics in SJIA showed that JADAS remission was reached by up to half of the patients while up to two-thirds reached JADAS minimal disease activity after 6 months on biological therapy [179]. In an observational study, Simonini et al. recently reported that children with SJIA had the lowest probability of flares after drug discontinuation when compared to the other JIA categories [180]. ANK, CNK, and TCZ have been included in recently developed clinical practice recommendations and treatment plans [145, 181, 182].

Patients whose disease is refractory to IL-1 therapies may respond to IL-6 inhibitors and vice versa [183]. Although many patients respond to IL-1 and IL-6 inhibition, a subset of patients continues to have refractory SJIA. These patients may benefit from abatacept [184]; anecdotal reports show that combination biological therapy may be successful in the treatment of refractory cases [185, 186].

Although its use has decreased since the advent of effective biologic agents, autologous Stem Cell Transplantation represented an option for severe, refractory cases of SJIA during the nineties, when anti-IL-1 and anti-IL-6 therapies were not available. Theoretically, the procedure leads to a resetting of the immune system and recovery of regulatory T cells [187]. High associated morbidity and mortality (due to MAS or infections) led to gradual discontinuation of this therapeutic procedure, which is now reserved for patients whose disease is refractory to conventional and biologic therapies [187, 188].

Potentially useful therapies are being investigated. Multipotent mesenchymal stromal cell therapy is relatively safe and has immunomodulatory properties, making it appropriate for the treatment of multi-refractory, immune-mediated disorders [189]. Preliminary studies have shown its efficacy in SJIA [190]. Likewise, inhibition of Janus kinase (JAK) through the use of JAK-inhibitors may prove efficacious in SJIA [191]. The efficacy and safety of Tadekinig alfa (a recombinant IL-18 binding protein [IL-18BP]) in AOSD was assessed in a recent phase II clinical trial [192]. The agent was reasonably safe and effective and might become a therapeutic option for SJIA in the future.

There is no current consensus on the optimal management of SJIA-associated MAS, which requires a rapid and intense treatment oriented at controlling the underlying disease activity. The combination of high dose intravenous corticosteroid pulses and cyclosporine has shown efficacy [193]. While the HLH treatment protocols developed by the Histiocyte Society [194] are progressively being abandoned by pediatric rheumatologists, early addition of ANK at higher doses, which has proven to be effective in several published cases, is becoming a preferred choice [131, 195]. Potential targets in MAS are IFN-γ and IL-18. Emapalumab, anti-*interferon-gamma* (IFN-γ) *monoclonal antibody*, *is being currently investigated as an agent to treat primary HLH* (ClinicalTrials.gov Identifier: NCT03312751), and it could be useful for the treatment of SJIA-associated MAS. Inhibition of IFN-γ has been effective in the treatment of MAS associated with the monogenic autoinflammatory disease, NLRC4-MAS [196]. On the other hand, the therapeutic use of rIL-18BP has also been effective in a patient with NLRC4-MAS [197]. Further research is needed to determine the clinical utility of these new agents in SJIA.

5.12 Disease Course and Prognosis

Classically, the disease course pattern of SJIA is classified into monocyclic (a single phase lasting up to 24 months), polycyclic (disease flares separated by months or years of inactive disease) or persistent (chronic persistent arthritis requiring treatment often into adulthood) [198, 199]. According to published series, these courses

have variable frequencies: monocyclic 11–45%, polycyclic 7–35%, and persistent 51–55% [200, 201]. Similarly, the disease may show persistently active systemic features ("systemic" course) or it may progress into an exclusively arthritic, often resistant and destructive disease ("polyarticular" course). This course progression is probably related to the abnormalities occurring sequentially in the innate and, later, in the adaptive immune system components [21, 199]. However, flares that include active systemic symptoms may occur, even after years of remission or purely arthritic involvement. Patients with very early onset (before age 18 months) are characterized by a serious and aggressive disease course [15].

SJIA patients often suffer from chronic disability and significant functional impairment. In adult life, patients who had been diagnosed as SJIA often exhibit severe disability and frequently need joint replacement [202]. Disability is proportional to the disease duration and affects a greater proportion of patients with longer follow up [117, 124, 203]. Predictive factors for poor functional capacity and/or joint damage are persistently active systemic features, use of corticosteroids and thrombocytosis at 6 months after onset, male sex, polyarticular involvement, cervical and hip involvement, and younger age at onset [204–210]. The course and outcome are variable, ranging from good in the monocyclic course to a more serious, progressive disease carrying considerable morbidity and mortality in the persistently active disease [15, 198, 199, 201].

However, nowadays clinically inactive disease and sustained remission are attainable in a significant proportion of cases [211, 212].

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Adult-Onset Still's Disease

6

Stéphane Mitrovic, Eugen Feist, and Bruno Fautrel

6.1 Introduction

Adult-onset Still's disease (AoSD was first described in the early 1970s, by Bywaters, as an inflammatory condition occurring in young adults. The disease was very similar to childhood-onset Still's disease, today called systemic-onset juvenile idiopathic arthritis (SoJIA), described a century ago by Sir Still [1]. Although the exact pathogenic mechanisms of the disease remain unknown, substantial advances have been made first to confirm the homology between AoSD and SoJIA, and then the disease became the archetype of nonfamilial, or sporadic, systemic autoinflammatory disorders (SAID) [2–4].

By definition, AoSD affects people older than 16, either de novo or those with a history of systemic JIA [3, 5, 6]. In the latter, a disease-free interval between the

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childhood episode and the adulthood recurrence differentiates AoSD from persistent SoJIA. In most patients, AoSD is characterized by four cardinal symptoms: spiking fever, an evanescent salmon-pink maculopapular rash, arthritis, and a white blood cell count (WBC) $\geq$10,000/mm^3, mainly neutrophilic polymorphonuclear cells (PMNs). Other features are sore throat or pharyngitis, myalgia, lymph node or spleen enlargement, pleuritis or pericarditis, multivisceral involvement, elevated levels of liver enzymes, and other hematologic abnormalities [3, 7, 8]. None of these symptoms is disease specific, so diagnosis of AoSD is difficult, and clinicians must first rule out neoplastic, infectious, or inflammatory conditions.

6.2 Epidemiology

To date, epidemiologic data about AoSD have been scarce and imprecise, because of the heterogeneous clinical presentation of the disease and the complex assessment of diagnosis. The disease occurs worldwide, and no specific familial aggregation has been reported. AoSD satisfies the definition of an orphan disease because historically its prevalence was estimated between one case per million in Europe [9] and ten cases per million in Japan [10]. In the Japanese study, the incidence was estimated at about one case per million in the mid-1990s. However, because of the substantial advances in AoSD diagnosis as well as differential diagnoses during the last two decades, these prevalence and incidence estimates lack robustness, and new studies are clearly needed to update these figures.

Initially, the disease was characterized as affecting exclusively young adults (i.e., 16–35 years of age [1]); however, more recent series identified cases in adults older than 35 and even elderly people [5, 11–14]. The sex ratio is almost balanced, with only a slight female predominance [5, 6, 11, 13–15].

6.3 Clinical Expression

6.3.1 AoSD Clinical Symptoms

AoSD is traditionally characterized by four "cardinal" symptoms (three are clinical, one is biological), with many other manifestations possibly associated [3, 7, 16].

6.3.1.1 Cardinal Symptom 1: Fever

Fever is constant when the disease is active, except in patients with established disease, for whom residual inflammation could remain without it. Typically, fever starts suddenly, and temperature rapidly reaches 39 °C or more, associated with shivers. It evolves with daily evening spikes for more than a week (Fig. 6.1). Patients usually experience rapid deterioration of general health as well as significant weight loss. Of importance, fever may be the only clinical symptom of AoSD as a potential diagnosis in patients with fever of unknown origin [17].

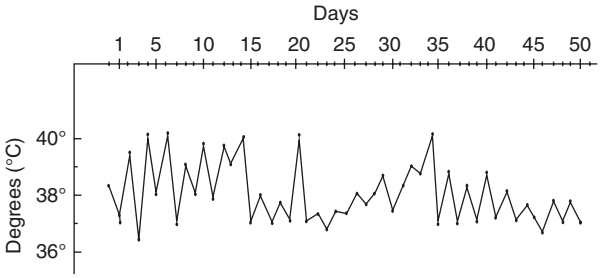

Fig. 6.1 Typical temperature curve during an AoSD flare

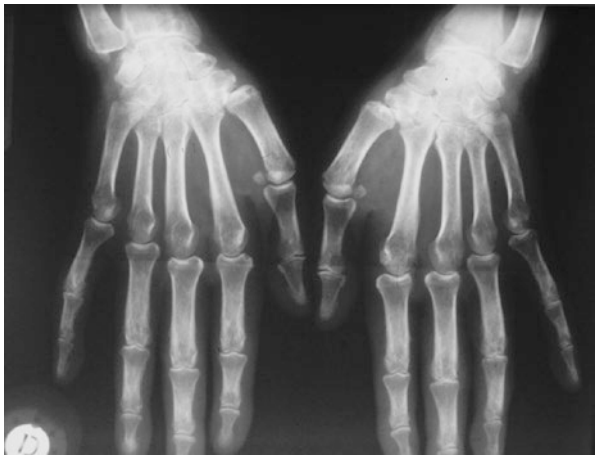

Fig. 6.2 Ankylosing carpal arthritis in adult-onset Still's disease

6.3.1.2 Cardinal Symptom 2: Arthralgia or Arthritis

Joint pain or arthritis is the second most common symptom, with synovitis, usually with concomitant fever spikes, occurring in more than two-thirds of patients. All joints can be involved, including sacroiliac and distal interphalangeal joints. In some patients, the presentation is that of a bilateral symmetrical rheumatoid arthritis (RA)-like polyarthritis [3, 7]. Synovial fluid analysis displays high cellularity, >2000 cells/mm^3, which confirms joint inflammation. When performed, synovium biopsy reveals only nonspecific synovitis. During the evolution, arthritis becomes erosive in one-third of patients; in these patients, isolated bilateral carpal ankylosis (i.e., without structural damage of metacarpophalangeal or proximal interphalangeal joints, in contrast to RA) is very suggestive of AoSD (Fig. 6.2) [1, 3, 7].

6.3.1.3 Cardinal Symptom 3: Skin Rashes

Skin rash is typically salmon pink-colored macular or maculopapular (Figs. 6.3 and 6.4). The rash is transient, mainly visible during fever spikes on the proximal limbs or trunk, and rarely involves the face, palms, or soles of the feet [3, 7, 18]. No specific histological feature has been described. Misdiagnosis with drug allergy is frequent and usually attributed to nonsteroidal anti-inflammatory drugs (NSAIDs) prescribed for joint symptoms or fever. Complete regression without scars is the rule.

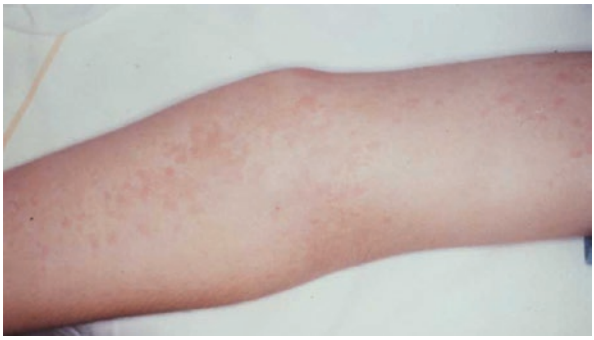

Fig. 6.3 Typical rash of the arm in adult-onset Still's disease

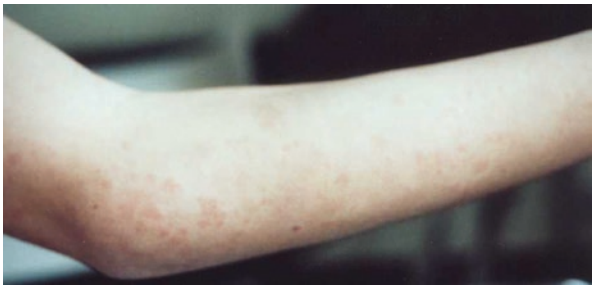

Fig. 6.4 Transient erythema of the elbow in adult-onset Still's disease

Atypical patterns also reported are urticarial or pruritic with dermographism [3, 7, 18]. Presence of purpuric lesions should lead to urgent coagulation workup because these lesions are suggestive of the AoSD hematologic complications of hemophagocytic syndrome or reactive hemophagocytic lymphoproliferation (RHL), disseminated intravascular coagulation (DIC), or thrombotic microangiopathy (TMA), also called thrombocytic thrombocytopenic purpura or Moschcowitz syndrome [3, 7].

6.3.1.4 Other Clinical Symptoms

Sore throat (odynophagia) and sometimes pharyngitis are classical symptoms, concomitant with fever (and not just a few weeks previous, e.g., in post-streptococcal arthritis) [3]. All microbiological test results are negative. The presence of this symptom in such a systemic context seems to exclude lymphoma or another neoplastic disease [19].

Diffuse and symmetrical lymphadenopathy is possible, eventually associated with splenomegaly or even hepatomegaly. However, large and nonsymmetrical lymphadenopathy should lead to the exclusion of malignant lymphoma by biopsy: reactive polyclonal lymphoid hyperplasia is the usual pattern in AoSD [3, 7]. Kikuchi necrotizing lymphadenitis has been described in a few cases [20].

Myalgia is frequent, but myositis or polymyositis is exceptional [3, 7, 21, 22].

Finally, as in many other inflammatory disorders, nonspecific manifestations have been reported: abdominal pain related to deep lymphadenitis, aseptic peritonitis or rarely acute pancreatitis, pleural effusion or pericarditis, or interstitial lung infiltrates [3, 7].

6.3.2 AoSD Biological Abnormalities

6.3.2.1 Cardinal Symptom 4: Increased Leukocyte and Neutrophil Counts

A major increase in leukocyte and neutrophil counts is observed (i.e., leukocyte count >10,000–15,000/mm^3, with neutrophils >80%). Greatly increased counts, up to 50,000/mm^3, can be observed, associated with myelemia. Leucopenia has also been described, in isolation or with anemia and/or thrombopenia; it often reveals RHL or TMA [3, 7].

6.3.2.2 Acute-Phase Reactants

Besides increased leukocyte and neutrophil counts, a substantial increase in acute-phase reactants—ESR and levels of CRP, fibrinogen, and serum immunoglobulins—is always present during AoSD flares.

6.3.2.3 Liver Function Tests

Elevated serum liver enzyme levels, rarely fulminant hepatitis, are often present, related to systemic inflammation or the use of drugs, such as antibiotics or NSAIDs, as symptomatic treatment before diagnosis.

6.3.2.4 Serum Ferritin and Glycosylated Ferritin

High serum ferritin level, an indicator of macrophage activation, has been frequently reported [5, 12, 23–26]. Although hyperferritinemia was first considered suggestive of AoSD, several studies showed that hyperferritinemia, whatever the threshold used, has poor positive predictive value in isolation without a suggestive context [27, 28].

Besides total ferritin level, the diagnostic performance of glycosylated ferritin (GF) level has been investigated [29]. The GF level normally represents more than half of the total ferritin level. In inflammatory conditions, the concentration of GF decreases and usually ranges from 20% to 50%; this decrease has been related to the saturation of glycosylation mechanisms due to hyperferritinemia. However, in AoSD, GF level is typically markedly decreased (below 20%), which suggests a more specific phenomenon. More extensive data revealed a sensitivity and specificity of GF ≤20% for AoSD diagnosis of 78% and 64%, respectively [27]. The combination of both hyperferritinemia and GF level ≤20% yielded a sensitivity and specificity of 67% and 84%, respectively. Of note, although serum ferritin level fluctuates according to systemic inflammation, GF level remains low several weeks to several months after disease remission [30]. However, as mentioned previously, low GF level is not completely specific to AoSD and is observed in other inflammatory processes, such as severe systemic infections [27]. Moreover, the GF level is usually low, ≤20%, in hemophagocytic syndromes, regardless of the cause, such as infection, neoplasm, or inflammation [31–33].

6.3.2.5 Immunological Findings

Results of immunological workups performed to exclude other connective tissue diseases or inflammatory joint diseases must be negative.

6.4 Pathogenesis

6.4.1 A Systemic Autoinflammatory Disorder as Opposed to a Systemic Autoimmune Disease

Approximately ten years ago, McGonagle and McDermott formulated the hypothesis of two main pathogenic mechanisms underlying immune-mediated inflammation against the self and proposed a new classification for immunological diseases contrasting autoimmunity and autoinflammation [2, 34]. Autoimmunity referred to adaptive immunity and was defined as aberrant dendritic, B- and T-cell responses in primary and secondary lymphoid organs leading to tolerance break and development of immune reactivity toward native antigens (with autoantibodies in most cases), whereas autoinflammation referred to innate immunity and was defined as dysregulated activation of macrophages and neutrophils in response to a danger signal leading to tissue damage. These categories represent a continuum, which allowed for a new classification of immune-mediated inflammatory disorders that was refined in the following years [2, 4].

Although autoimmune diseases were rather easily diagnosed based on autoantibody or autoantigen-specific T and B cells, no specific biomarker exists for SAID. The definition mainly relies on similarities with monogenic, hereditary periodic fever syndromes, which were at the origin of the concept. They include several key features: intense inflammation with periodic fever, tissue inflammation depending on the disease, increased leukocyte and neutrophil count, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, and, more recently, a pathogenic role of inflammasome and response to interleukin-1 (IL-1) blockade [35]. Besides monogenic familial syndromes, Crohn's disease was the first nonfamilial polygenic AID, mainly tissue specific, with predominant gut involvement [36, 37]. A few years later, Still's disease was described as another nonfamilial AID, becoming one of the most characteristic polygenic systemic SAID [3].

6.4.2 A Pro-inflammatory Cascade

The mechanisms underlying AoSD pathogenesis are largely hypothetical, but, from the evident pathogenic pathway seen in SoJIA patients and the growing understanding of SAID, a pro-inflammatory cascade can be proposed (Fig. 6.5) [3, 7, 16, 38, 39].

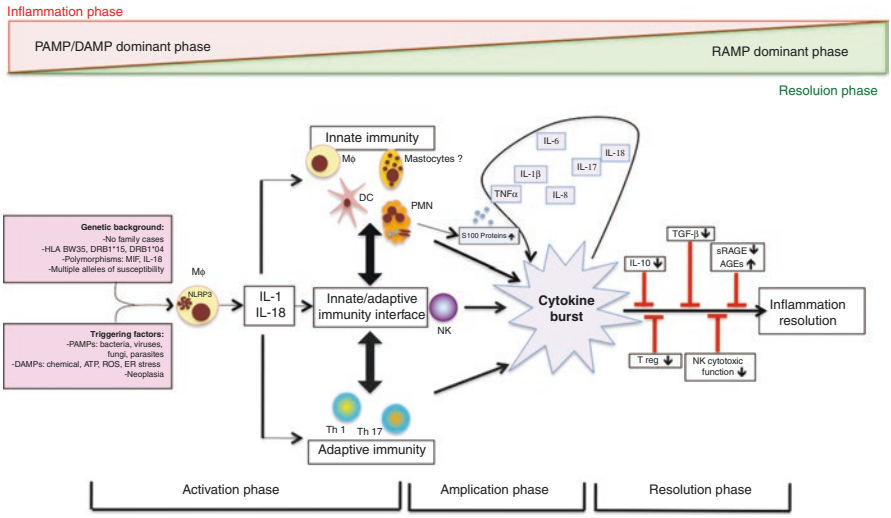

Fig. 6.5 Pathogenic pathways involved in AoSD (adapted from [16]). *AGE* advanced glycosylated end products, *ATP* adenosine triphosphate, *ER* endoplasmic reticulum, *DAMP* damage-associated molecular pattern, *DC* dendritic cells, *HLA* human leukocyte antigen, *IL* interleukin, *MΦ* macrophages, *MIF* macrophage inhibitory factor, *NK* natural killer, *PAMP* pathogen-associated molecular pattern, *PMN* polymorphonuclear neutrophil, *RAMP* resolution-associated molecular pattern, *ROS* reactive oxygen species, *sRAGE* soluble receptors of AGE products, *TGF* transforming growth factor, *Th1* T-helper 1 cells, *Treg* T-regulatory cells

6.4.2.1 A Cytokine Storm

The starting point is likely specific danger signals, such as pathogen- or damage-associated molecular patterns (i.e., PAMPs or DAMPs). Danger signals are transmitted to macrophages and neutrophils via specific Toll-like receptors that activate specific inflammasomes, likely NOD-like receptor family pyrin domain containing 3 (NLRP3), leading to caspase activation and overproduction of active IL-1 [39–42]. This step seems to be central to the AoSD pathogenesis and leads to intense innate immune cell activation and overproduction of several pro-inflammatory cytokines including IL-6, IL-18, tumor necrosis factor (TNF), as well as IL-8 and IL-17. Several factors actively contribute to an amplified inflammatory response, often referred to as the cytokine "burst" or "storm" [3, 42]. In addition to IL-1 itself, conferring retrograde activation of macrophages and neutrophils; different alarmins, such as the S100 protein—S100A12 protein seeming to be more specific to Still's disease in children—and advanced glycosylated end (AGE) products are involved in these processes [39, 42–46]. Besides amplification mechanisms, SAID pathogenesis has been suggested to involve deficiency or failure in regulatory or anti-inflammatory mechanisms: deficiency in T regulator or natural killer cells, insufficient IL-10 production, and deficiency in resolution lipid mediators, soluble receptors of AGEs (RAGEs), or other resolution-associated molecular patterns [47–50].

6.4.2.2 A Role for Infections as a Trigger

Bacteria or viruses are the usual suspects for the danger signals. Numerous case reports describe the occurrence of AoSD after viral infection (rubella; measles; mumps; Epstein-Barr virus; hepatitis A, B, or C virus; HIV; cytomegalovirus; parvovirus B19; adenovirus; echovirus; human herpes virus 6; influenza and parainfluenza viruses; Coxsackie virus) or bacterial infection (*Yersinia enterocolitica*, *Campylobacter jejuni*, *Chlamydia trachomatis* or *pneumoniae*, *Mycoplasma pneumoniae*, *Borrelia burgdorferi*) [3, 7, 39]. In addition, patients often experience odynophagia or pharyngitis just before the start of the disease or the relapse, which could correspond to the infectious danger signal that will trigger Toll-like receptors and start the intense inflammatory process.

6.4.2.3 A Role for a Genetic Background

In contrast to monogenic, hereditary, periodic fever syndromes, the underlying genetic background of AoSD is largely unknown. The disease is present in different geographic regions and different ethnic groups [3, 4, 7, 39, 51]. Association studies have suggested a potential predisposing genetic background. HLA-Bw35 was the first identified as a susceptibility antigen and associated with a mild self-limiting pattern of the disease [52]. HLA-DR4 was found more prevalent in AoSD cases versus healthy controls, and HLA-DRw6 was associated with the occurrence of proximal arthralgia [53]. However, no functional analysis has confirmed these hypotheses [3, 39, 53].

Recently, two major findings have been reported in SoJIA patients. Firstly, a homoallelic missense mutation in the enzyme laccase (multicopper oxidoreductase) domain-containing 1—*LACC1*—has been identified in 13 SoJIA patients from five Saudi consanguineous families [54]. Although familial SoJIA is not the rule, this study raises the potential role of this laccase in the pathogenesis of SoJIA. Secondly, a large association study performed in 982 SoJIA children and 8010 healthy controls identified a strong association between SoJIA and different HLA-DRB1*11 haplotypes which all contain glutamate 58 [55]. This finding is more challenging since it would involve adaptive immunity in the AoSD pathogenesis which was not expected [56].

Finally, substantial advances have been made in exploring the human genome, which will facilitate the identification of potential mutations in genes involved in autoinflammatory pathways, including de novo germinal mutations or somatic mutations occurring during fetus development or after birth [57, 58].

6.5 Atypical Forms and Life-Threatening Complications

Several severe manifestations have been described in AoSD, which explains the potentially pejorative prognosis of the disease [3, 59]. The disease can be life-threatening because of the predominant involvement of one organ or of systemic complications with multiple organ failure from the outset, while the diagnosis isn't

clearly confirmed. The articular signs may often fall by the wayside because of the gravity of the complications of such clinical forms, which can contribute to misdirect the clinicians who are not familiar with AoSD.

These complications are given in Table 6.1, and the most frequent and relevant ones are discussed in more detail.

6.5.1 Reactive Hemophagocytic Lymphohistiocytosis (RHL)

This is a common complication of AoSD at the time of diagnosis, right after treatment introduction or during the course of the disease. In systemic-onset JIA, it is also called macrophage activation syndrome. This serious complication should be suspected in a patient with persisting fever (in contrast to evening spiking fever) and decrease in initially elevated leukocyte and neutrophil counts [3, 32, 59]. Several other manifestations can be associated.

The key issue with RHL is to determine whether its occurrence is related to AoSD intense inflammation or to concomitant infection, potentially favored by immunomodulators introduced because of AoSD. The list of possible infections is quite long, with viral reactivation at first place.

6.5.2 Coagulation Disorders

AoSD can be complicated by two serious coagulation disorders, mainly at the acute phase of the disease.

The first disorder, disseminated intravascular coagulation (DIC), is not rare and may occur at a frequency of 1–5% [8, 53, 59–67]. This diagnosis should be suspected with the combination of thrombotic events and cutaneous or mucosal bleeding and sometimes specific organ involvements, such as fulminant hepatitis, cardiac or respiratory failure, or stroke. Hemostasis workups reveal platelet and coagulation factor consumption, increased thromboplastin time, and high D-dimer levels.

The other rare but quite severe coagulation disorder is thrombotic microangiopathy (TMA). It must be suspected with unexplained multiorgan failure or stroke, related to multiple small thrombi leading to tissue ischemia and mechanical hemolytic anemia [60, 74, 75]. Acute vision impairment, such as blurred vision related to Purtscher-like retinopathy, is frequently the first symptom [74]. Key diagnostic tests display thrombocytopenia by platelet consumption, anemia, and schistocytes (fragmented red blood cells), which are specific to this diagnosis. Organ imaging may reveal multiple infarctions. In addition, ADAMTS13 enzymatic activity needs to be tested because acquired deficiency has been found to predispose to TMA [59, 96–98]. TMA has been mainly described during AoSD flare, related to intense inflammation or to concomitant infection with Shiga toxin-producing microorganisms [74].

Table 6.1 Main life-threatening complications of AoSD

Complications	Signs and symptoms	Diagnosis	Treatment	References
Reactive hemophagocytic lymphohistiocytosis (RHL)	• High (>38.5 °C), persistent fever[a] • Peripheral lymphadenopathy, hepatomegaly, splenomegaly • Polymorphous skin rashes[b]: rashes, edema, petechiae, urticaria, or purpura • Multiple organ involvement: pulmonary, neurological, gastrointestinal, or renal involvement, bleeding • Rapid change on hemogram: resolution of high leukocyte and neutrophil counts, occurrence of anemia and thrombocytopenia	• Cytopenia[c]: anemia, thrombocytopenia, and/or leukopenia • Decreased ESR[d] • Increased liver function tests: transaminases and alkaline phosphatases • Elevated LDH level • Hypertriglyceridemia • Hyperferritinemia[e] • High soluble CD25 or CD163 level • Hemophagocytosis in bone marrow smear (or reticuloendothelial organs) • Increased CD163 staining in bone marrow Or • HScore[f]	• Supportive care in ICU • Exclusion of an additional trigger: mainly infections[g] • Immunomodulatory agents: – High-dose corticosteroids – ±IL-1 or IL-6 inhibitors after a few days – If refractory, etoposide or cyclosporine A	[3, 32, 59]
Disseminated intravascular coagulopathy (DIC)	• Hematoma, bleeding • Thrombotic event • Multi-organ involvement or failure: ARDS, pleural effusion, myocarditis, pulmonary embolism, gastrointestinal bleeding, CNS involvement	• Thrombocytopenia • Prolongation of prothrombin time and activated thromboplastin time • Decreased fibrinogen • Increased levels of fibrin degradation products	• Supportive measures in ICU • Immunomodulatory agents: – High-dose corticosteroids – ±IL-1 or IL-6 inhibitors – If refractory, cyclosporine A	[8, 53, 59–73]

Complications	Signs and symptoms	Diagnosis	Treatment	References
Thrombotic microangiopathy (TMA) or Moschcowitz syndrome	• Acute vision impairment (early sign) • Weakness • Confusion, seizures, or coma • Abdominal pain, nausea, vomiting, diarrhea • Cutaneous gangrene • Arrhythmias caused by myocardial damage • Multi-organ failure	• Mechanical hemolytic anemia (schistocytes on the peripheral blood smear with a negative Coomb's test) • Thrombocytopenia • Multiple organ failure of varying severity (mainly the kidneys and the CNS)	• Supportive measures in ICU • Specific treatment: – High-dose corticosteroids and plasma exchange – ±Hemodialysis – If insufficient, multidisciplinary round ±IL-1 or IL-6 inhibitors or cyclosporine or IVIG	[60, 74–76]
Fulminant hepatitis	• Physical status deterioration: appetite loss, fatigue • Jaundice • Hepatomegaly • Right abdominal pain • Rarely, bleeding • Elevated liver function test findings	• Abnormal and rapidly increasing liver function test findings • High activity on multi-biomarker FibroTest • Liver biopsy (if performed): nonspecific portal infiltrates of lymphocytes, plasma cells, and neutrophils, hepatocytic lesions or massive necrosis	• Supportive measures in ICU • Discontinuation of all potentially hepatotoxic drugs[h]: mainly acetaminophen, aspirin, NSAIDs, or methotrexate • Rule out RHL, DIC, and/or TMA • Rule out viral reactivation • Specific treatment: – High-dose corticosteroids – ±IL-1 or IL-6 inhibitors[i] or cyclosporine • Liver transplantation in extreme cases	[42, 60]
Cardiac complications	• Pericarditis, sometimes recurrent • Tamponade • Myocarditis • Endocarditis (exceptional cases)	• Electrocardiography • Echocardiography • Troponin and creatinine kinase level increase if myocarditis	• Supportive measures in ICU • Specific treatment: – High-dose corticosteroids usually – ±IL-1 or IL-6 inhibitors	[42, 60]

(continued)

Complications	Signs and symptoms	Diagnosis	Treatment	References
Pulmonary arterial hypertension	• Dyspnea (key symptom) • Fatigue, dizziness • Syncope • ARDS	• Electrocardiography: right atrium hypertrophy • Echocardiography: systolic PAP >35 mmHg • Right heart catheterization (gold standard): – Mean PAP ≥25 mmHg at rest – End-expiratory PAWP ≤15 mmHg – Pulmonary vascular resistance >3 wood units	• Close monitoring and refer to a pulmonary hypertension reference center (multidisciplinary rounds) • Vasodilatation therapy: calcium channel blockers, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and/or prostacyclin analogues • Immunosuppressive therapy: – High-dose steroids – ±IL-1 or IL-6 inhibitors or cyclosporine	[77–88]
Pulmonary complications	• Pleuritis • Interstitial lung disease with or without ARDS • Aseptic empyema • Diffuse alveolar hemorrhage	• High-resolution computed tomography • Bronchoalveolar lavage (for differential diagnosis: in AoSD, nonspecific neutrophilic profile) • Pulmonary function tests	• Supportive measures in ICU if ARDS • Rule out differential diagnoses: infections, cardiogenic causes (brain natriuretic peptide dosage, echocardiography), drug-related or iatrogenic causes, cancer • Specific treatment: – High-dose corticosteroids usually – ±IL-1 or IL-6 inhibitors	[42, 60]
AA amyloidosis	• Exceptional these days • Renal failure, proteinuria, edema, hydrops • Digestive involvement • Orthostatic hypotension, other neuropathies	• Biopsy of minor salivary gland, or abdominal fat pad, or the kidney	• Inflammation control with IL-1 or IL-6 inhibitors	[89–93]

AoSD adult-onset Still's disease, *ARDS* acute respiratory distress syndrome, *BAL* bronchoalveolar lavage, *CNS* central nervous system, *DIC* disseminated intravascular coagulopathy, *DRESS* drug reaction with eosinophilia and systemic symptoms, *ESR* erythrocyte sedimentation rate, *ICU* intensive care unit,

IL interleukin, *IVIG* intravenous immunoglobulins, *LDH* lactate dehydrogenase, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PAP* pulmonary arterial pressure, *PAWP* pulmonary artery wedge pressure, *RHL* reactive hemophagocytic lymphohistiocytosis, *TMA* thrombotic microangiopathy

[a]Whereas in AoSD, fever is often remitting, with spikes (hectic)

[b]Whereas in AoSD, skin rash is classically maculopapular and evanescent

[c]Whereas in noncomplicated AoSD, white blood count is often ≥10,000/mm^3, with mainly neutrophils, and thrombocytosis is frequent

[d]Whereas in noncomplicated AoSD, ESR is high

[e]Hyperferritinemia is also seen in AoSD, but, in case of very high ferritin levels or sudden increase, an RHL or another systemic complication should be suspected

[f]This scoring system is a set of nine weighted criteria (known underlying immunosuppression, temperature, organomegaly, number of cytopenia, ferritin, triglyceride, fibrinogen, serum glutamic oxaloacetic transaminase, hemophagocytosis features on bone marrow aspirate) that have been elaborated and validated for the diagnosis of RHL in adults [94]. It is freely available online (http://saintantoine.aphp.fr/score/)

[g]Mainly infections, in particular viral reactivation (Epstein-Barr virus, cytomegalovirus), which may trigger AoSD or reactivated by immunosuppressive treatments

[h]Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, potentially induced by interleukin (IL)-1 or IL-6 or another immunosuppressive agent, is a differential diagnosis that should always been ruled out because it can be responsible for a fulminant hepatitis and mimic AoSD systemic manifestations

[i]Keeping in mind that tocilizumab-induced hepatic injury has also been reported [95]

6.5.3 Cardiac and Pulmonary Involvements

Although pleural effusion or pericarditis is frequent, other serious cardiac or pulmonary manifestations have been described.

Specific attention should be dedicated to a rare and very severe AoSD manifestation, pulmonary arterial hypertension (PAH), with several cases recently reported [77–88]. PAH, either idiopathic or occurring with AoSD or other connective tissue diseases, is thought to be related at least in part to immune-related alteration of the endothelium with overproduction of IL-1, IL-6, IL-18, and TNF [79, 80, 82, 83, 99]. PAH may occur at AoSD onset or later and seems to predominate in women. The diagnosis must be suspected with unexplained and often rapidly progressing dyspnea [59, 79, 81, 100, 101]. Electrocardiography is rarely contributive, eventually disclosing signs of right atrium hypertrophy. Echocardiography is more useful for detection by measuring systolic pulmonary artery pressure, which is >35 mmHg, and the exclusion of left ventricle dysfunction. The formal PAH diagnosis remains the right heart catheterization [100, 101].

6.5.4 Hepatitis

While liver abnormalities are most often limited to mild to moderate increases in aminotransferase activity which is frequent (up to 60% of cases), fulminant and fatal hepatitis have been reported [3, 59]. The potential role of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), or methotrexate has been mentioned by some authors [102]. Thus, clinicians should closely monitor liver function from the onset of the disease and particularly after prescription of potentially hepatotoxic drugs. Self-medication should be avoided.

Liver biopsy, if performed, reveals nonspecific portal infiltrates of lymphocytes, plasma cells, and polymorphonuclears [3, 59, 102]. Hepatocytic lesions or massive necrosis has been described in fulminant hepatitis with rapidly progressive hepatic insufficiency. Liver transplantation was necessary in a few exceptional cases [3, 103].

6.5.5 Exceptional Symptoms

Amyloid A amyloidosis is becoming extremely rare owing to the better ability of AoSD treatments to control inflammation [89–93]. It could be observed in refractory patients or in patients who did not have access to adequate treatments for long periods of time. Multiple organs can be involved.

Many other symptoms attributed to AoSD have appeared in the literature. As these are almost exclusively in case reports, drawing conclusions is difficult:

– Ophthalmologic involvement related to sicca syndrome, conjunctivitis, uveitis, or episcleritis [1, 5, 102].

– Neurological manifestations, such as ischemic stroke, aseptic meningitis, or encephalitis [3]. Such symptoms might reveal hepatic failure or coagulation dysfunction, as in DIC, RHL, or TMA.
– Renal involvement limited to isolated proteinuria or related to glomerular or interstitial nephritis [102, 103]. Acute renal failure is possible in the context of severe myositis, hepatic insufficiency, or hematological complications [21, 74, 102–104].
– Secondary amyloid A amyloidosis (AA amyloidosis) is nowadays exceptional and is related to sustained uncontrolled inflammation [89–93].

6.6 Differential Diagnoses

AoSD is an exclusion diagnosis. Because of presentation heterogeneity and of the lack of specificity of the clinical and biological manifestations, many other diagnoses might be evoked and afterward ruled out, before reasonably considering AoSD(Table 6.2) [3, 5, 6, 102]. Before finally diagnosing AoSD, it is thus essential to first rule out neoplastic, infectious, or inflammatory conditions that can mimic the disease.

Table 6.2 Differential diagnoses of AoSD and helpful tests to rule them out

	Diseases	Relevant workups
Infections		
Bacteria	Pyogenic bacterial septicemia	Blood cultures, PCT
	Infectious endocarditis	Echocardiogram
	Biliary, colic, or urinary occult infections, tuberculosis	CT scan IGRAs, CT scan
	Brucellosis, yersiniosis	Biopsy for bacteriology and histology Serology, PCR
Viruses	HIV, viral hepatitis Parvovirus B19 Herpesviridae Measles, rubella	Serology, PCR
Parasites	Toxoplasmosis, abscessed parasitosis	Serology, PCR
Malignant diseases		
Hematological disease	Hodgkin's disease or non-Hodgkin's lymphoma	Biopsy of a large and asymmetrical lymphadenopathy
	Angioimmunoblastic lymphadenopathy	Bone marrow smear or biopsy
	Castleman's disease	CT scan
	Myeloproliferative disorders	PET/CT scan
Solid cancers	Kidney, colon, lung, etc. Paraneoplastic syndromes	CT scan, PET/CT scan

(continued)

Table 6.2 (continued)

	Diseases	Relevant workups
Systemic diseases		
Autoimmune diseases	Systemic lupus erythematosus	Antinuclear autoantibodies
	Polymyositis, dermatomyositis	CPK, specific autoantibody, biopsy
	Rheumatoid arthritis	RF, ACPA, joint ultrasonography
	Polyarteritis nodosa or other vasculitides	ANCA, arteriography
Autoinflammatory disorders	Hereditary autoinflammatory syndromes:	Familial history and
	– Familial Mediterranean fever	– MEFV gene sequencing
	– Mevalonate kinase deficiency	– Urinary mevalonic acid, MVK gene sequencing
	– TNF receptor-associated periodic syndrome	–TNFRSF1A gene sequencing
	– Cryopyrin-associated periodic syndromes	– CIAS1 (NLRP3) gene sequencing
	Neutrophilic dermatosis, Sweet syndrome	Skin biopsy
Other	Post-streptococcal arthritis	ASLO
	Reactive arthritis	No fever, erythema nodosum
	Sarcoidosis	ACEs, lesion biopsy (granulomatosis)
	Schnitzler's syndrome	Monoclonal gammopathy
	Kikuchi-Fujimoto disease	Biopsy of a large and asymmetrical lymphadenopathy
	Drug-related hypersensitivity	Eosinophilia, drug investigation

ACEs angiotensin-converting enzymes, *ACPA* anti-citrullinated antibody, *ANCA* anti-neutrophil cytoplasmic antibodies, *ASLO* anti-streptolysin O antibody, *CPK* creatine phosphokinase, *CT* computed tomography, *HLA* human leukocyte antigen, *IGRAs* interferon gamma release assays, *MEFV* Mediterranean fever virus, *MVK* mevalonate kinase, *PCR* polymerase chain reaction, *PCT* procalcitonin, *PET* positron emission tomography, *RF* rheumatoid factor, *TNFRS1A* tumor necrosis factor receptor superfamily member 1A

6.6.1 Infections

Infectious diseases represent the most complex issue in differential diagnoses because AoSD therapies can be highly deleterious. The most misleading diagnoses are probably deep occult infections (e.g., biliary tract abscess or bone marrow infestation) or subacute endocarditis [3]. Whole blood culture, urine testing, and synovial fluid culture seem the minimal workup, while other tests might be considered depending on the context.

6.6.2 Malignant Diseases

Among malignancies, malignant lymphomas—either Hodgkin's disease or non-Hodgkin's lymphomas—are probably the most misleading and the first to exclude

if nonsymmetrical, fixed, and indurated lymph node enlargement is present [3, 105]. Less frequently, systemic inflammatory conditions have been described in the course of lymphoid leukemia or in paraneoplastic syndromes associated with solid cancers of either the lung or the breast [3, 105].

6.6.3 Autoimmune or Autoinflammatory Disorders

Autoimmune diseases that can mimic AoSD include vasculitis, especially polyarteritis nodosa, and polymyositis [6]. For patients with mainly chronic arthritis, the distinction between seronegative RA and AoSD can be difficult.

Besides autoimmune diseases, hereditary or nonfamilial autoinflammatory syndrome (AIS) can present with symptoms close to AoSD because of the combination of fever, skin lesions, and arthritis in addition to other symptoms that differ among the AIS [106–108]. Although the hereditary AIS often begins during childhood, the diagnosis tends to be made when the individual is an adult; examples are hyperimmunoglobulin D (IgD) syndrome or TNF receptor-associated periodic syndrome (TRAPS). Different mutations have been associated with different hereditary AIS, but, to date, none has been associated with AoSD. However, the similarities between these diseases and AoSD might suggest common pathogenic pathways and place AoSD as a nonfamilial, sporadic form of AIS.

Finally, in rare cases, the severe and systemic drug hypersensitivity reaction can mimic AoSD. The presence of urticarial skin lesions and increased eosinophilic PMN count are suggestive features, as is exposure to a potential agent within the previous days or weeks.

6.7 Classification Criteria and Biomarkers

After comprehensive investigations, no clinical sign or biological abnormality can be considered AoSD specific enough to ascertain the diagnosis. Thus, classification criteria may be helpful, although they have been developed more for clinical research than diagnosis.

6.7.1 Classification Criteria

Two sets of criteria have been validated (Table 6.3). The Yamaguchi criteria set, published in 1992, is the most widely used [109]; however, it contains exclusion criteria that are problematic in clinical practice. The Fautrel criteria set has the advantage of including ferritin and GF levels as diagnostic biomarkers and does not require exclusion criteria [13]. In a recent validation study, both sets showed high sensitivity and specificity [14].

Table 6.3 Classification criteria for adult-onset Still's disease

Yamaguchi et al. [109]	Fautrel et al. [13]
Major criteria	
1. Fever ≥39 °C lasting 1 week or more 2. Arthralgia lasting 2 weeks or more 3. Typical skin rash: maculopapular, nonpruritic, salmon-pink rash with concomitant fever spikes 4. Leukocytosis ≥10,000/mm^3 with neutrophil polymorphonuclear count ≥80%	1. Spiking fever ≥39 °C 2. Arthralgia 3. Transient erythema 4. Pharyngitis 5. Neutrophil polymorphonuclear count ≥80% 6. Glycosylated ferritin fraction ≤20%
Minor criteria	
1. Pharyngitis or sore throat 2. Lymphadenopathy and/or splenomegaly 3. Liver enzyme abnormalities (aminotransferases) 4. Negative for rheumatoid factor or antinuclear antibodies	1. Typical rash 2. Leukocytosis ≥10,000/mm^3
Exclusion criteria	
1. Absence of infection, especially sepsis and Epstein-Barr viral infection 2. Absence of malignant diseases, especially lymphomas 3. Absence of inflammatory disease, especially polyarteritis nodosa	None
At least five criteria, including two major criteria *And* *No exclusion criteria*	*Four major criteria* *Or* *Three major criteria and two minor criteria*
Classification performance[a] Se, 96.3%; Sp, 98.2%; PPV, 94.6%; NPV, 99.3% *Modified Yamaguchi criteria* *Yamaguchi criteria and* – *Ferritin* > *N*:Se, 100%; Sp 97.1%; PPV, 87.1%; NPV, 100% – *GF* ≤ *20%*:Se, 98.2%; Sp, 98.6%; PPV, 93%; NPV, 99.6%	*Classification performance*[a] Se, 87.0%; Sp, 97.8%; PPV, 88.7%; NPV, 97.5%

[a]Lebrun D et al. Semin Arthritis Rheum 2018 [14]

6.7.2 AoSD Biomarkers

The most relevant serum biomarkers identified to date are listed in Table 6.4.

6.7.2.1 Biomarkers for Routine Clinical Setting

Ferritins are the major biomarkers for AoSD. Serum ferritin level is a key biomarker to assess disease activity, but probably less relevant for diagnosis since its specificity is limited and no clear threshold has been identified so far [27, 28]. The diagnostic value of glycosylated ferritin level, with the threshold of GF≤20%, is much more interesting [27, 30].

Table 6.4 Most relevant serum biomarkers identified to date in adult-onset Still's disease (AoSD) cohorts and their intended potential use

Biomarker	Diagnosis[a]	Disease activity monitoring	Prognosis: severity (i.e., predictive of life-threatening complications)	Prognosis: evolution (i.e., predictive of evolution pattern[b] (systemic versus arthritis; monophasic, recurrent, or progressive, either systemic or joint)	References
Routine biomarkers					
CRP	High sensitivity No specificity	+	−	−	[42]
Ferritins					
Ferritin >ULN ≥5ULN (≥1000 μg/L)	High sensitivity No specificity	+	+	±	[5, 12, 27, 28, 61, 110]
	Se 40.8% Sp 80%	+	+	High levels associated with systemic pattern[c]	
Glycosylated ferritin (GF) *≤20%*	Se 79.5% Sp 66.4%	−	+	NA	[29, 30]
Ferritin >ULN and GF *≤20%*	Se 70.5% Sp 83.2%	−	−	−	[29, 30]
Ferritin >5ULN and GF *≤20%*	Se 70.5% Sp 92.9%	−	−	−	[29, 30]
Calprotectin (S100A8/S100A9 proteins)	±[d]	+	NA	NA	[111, 112]
Procalcitonin	Weak (rule out sepsis)	NA	NA	NA	[113]
SAA	NA	NA	+ Predictive of AA amyloidosis	NA	[42]

(continued)

Biomarker	Diagnosis[a]	Disease activity monitoring	Prognosis: severity (i.e., predictive of life-threatening complications)	Prognosis: evolution (i.e., predictive of evolution pattern[b] (systemic versus arthritis; monophasic, recurrent, or progressive, either systemic or joint)	References
Nonroutine biomarkers					
IL-18 > 150 ng/L >366 ng/L	Se 88% Sp 78% Se 91.7% Sp 99.1%	+	+ High levels are associated with RHL, hepatitis, and steroid dependence	+ High levels potentially associated with systemic pattern	[110, 111, 114–124]
IL-1β*	–[e]	+	±	± High levels potentially associated with systemic pattern	[115, 116, 125]
IL-6*	–[e]	+	± High levels potentially associated with RHL	± High levels potentially associated with arthritis pattern	[115, 116]
TNF-α*	–[e]	–	–	–	[115, 116]
S100A12 protein*	±[f]	+	NA	NA	[43, 45, 126]
AGEs and sRAGE*	±	+	NA	+ Higher AGE levels in serum with polycyclic or chronic articular patterns (compared to monocyclic pattern)	[50]
CXCL10*	+	+	NA	NA	[127]
CXCL13*	+	+	NA	NA	[127]
sCD163*	±	NA	NA	NA	[128, 129]
MIF*	+	+	NA	NA	[130]
ICAM1*	±	+	NA	NA	[131]

+ yes, − no, ± tested but contradictory results, *NA* not assessed, *ULN* upper level of normal, *se* sensitivity, *sp.* specificity, ∗reference range according to manufacturer

AA amyloid A, *AGEs* advanced glycation end products, *CRP* C-reactive protein, *ICAM1* intracellular adhesion molecule-1, *IL* interleukin, *MIF* macrophage inhibitory factor, *RHL* reactive hemophagocytic lymphohistiocytosis, *SAA* serum amyloid A protein, *sRAGE* soluble receptors for AGEs, *TNF* tumor necrosis factor

[a]A good diagnostic biomarker helps rule out the differential diagnoses of infection, malignancy, and other inflammatory disorders

[b]Identifying the disease subset might orientate the therapeutic strategy

[c]Serum ferritin levels are significantly higher in the systemic subtype [110], but high ferritin levels after adequate treatment may predict chronic articular course [61]

[d]Calprotectin levels help rule out rheumatoid arthritis, but further studies are needed to validate it as a diagnostic biomarker because of no statistical difference between AoSD and septic patients, although the populations were small [42]

[e]Elevated plasma levels of IL-1β, IL-6, and TNFα have been found during AoSD, but the cytokine profile is not specific and cannot differentiate AoSD patients from those with sepsis

[f]S100A12 was found an efficient diagnostic and monitoring biomarker in systemic juvenile arthritis, but further studies are needed for validation in AoSD

Procalcitonin, a marker of severe systemic infection, was also found elevated in patients with active AoSD and does not appear relevant to distinguish acute infection from AoSD flare [42, 113].

Serum level of calprotectin (i.e., S100A8/S100A9 protein) could be an additional disease activity biomarker because alarmins seem to play a key role in AoSD pathogenesis. However, it is not specific to AoSD and may be elevated in many other inflammatory conditions [42, 44, 111, 112]. Finally, serum amyloid A protein (SAA) is an inflammatory biomarker found predictive of amyloidosis [42].

6.7.2.2 Potential Biomarkers for Future Clinical Research

Several research works assessed serum cytokine levels. High serum levels of IL-1, IL-6, and IL-18 have been found in systemic forms of AoSD and can be considered activity biomarkers. However, their additional value on top of CRP level and other inflammatory biomarkers is unclear, and these cytokines are clearly not specific to AoSD. Thus, they are not recommended in routine investigation. Of importance, IL-18 seems to play a key role in RHL.

AGE products and RAGEs, involved in AoSD pathogenesis, may be elevated in other inflammatory disorders. High serum levels have been associated with polycyclic or chronic/progressive evolution patterns [42]. Serum level of soluble CD163, a macrophage activation biomarker, is elevated in AoSD but is not specific to the disease. Finally, several chemokines (C-X-C motif chemokine ligands 10 and 13, macrophage inhibitory factor) have been found to be diagnostic biomarkers for AoSD, which needs to be confirmed in larger patient samples [42].

6.8 Disease Evolution and Prognosis

AoSD evolution can be quite diverse and currently is impossible to predict. Several patterns of evolution have been described, mainly based on case series and not robust epidemiological studies [5, 9, 102, 132, 133]:

6.8.1 Evolution Patterns

6.8.1.1 Self-Limited, Monocyclic Evolution

It combines systemic manifestations and joint involvement: the initial flare evolves over a few weeks; remission is achieved with steroids or other immunomodulatory agents after a few days or weeks; and treatments can be progressively tapered and then stopped without relapse after a few months. The pattern may represent 19–44% of cases.

6.8.1.2 Recurrent or Polycyclic Evolution

It is characterized by AoSD relapses after a few months or years, under immunomodulatory treatment or after its discontinuation. In this pattern, one classical presentation is a first flare during childhood-diagnosed SoJIA, followed by sustained drug-free remission for several years, and then a relapse in adulthood. In most of

these cases, recurrences combine systemic and joint involvement. The pattern represents 10–41% of cases.

6.8.1.3 Chronic and Progressive Evolution

In this form, a continuous inflammation is responsible for chronic and frequently erosive joint involvement with regular systemic flares. This pattern was the most frequent, estimated at 35–67% of cases, in old series [1, 102, 134]. Although no new estimates are available, this pattern should be less likely with the most recent targeted therapies.

6.8.2 Prognosis

The prognosis of AoSD is dominated by potential life-threatening events as well as progressive functional impairment.

6.8.2.1 Life Prognosis

The life prognosis is dominated by the severity of the following visceral involvements, in isolation or combination: hematological complications, such as DIC, TMA, or severe RHL; fulminant hepatitis with rapid liver failure; and acute respiratory distress syndrome, extensive myocarditis, or multiorgan failure [3, 59]. Importantly, exacerbation of these serious symptoms has been reported within the first days of treatment initiation, especially of biological therapies. This necessitates a close and very careful monitoring of such patients at the start of treatment. In addition to organ involvements, the development of secondary amyloidosis of the AA type remains possible in long-standing refractory chronic articular AoSD [59].

6.8.2.2 Functional Prognosis

Functional prognosis depends mainly on erosion and joint destruction in chronic articular AoSD, which affects approximately one-third of patients [3, 7, 102]. No clear predictor of erosive joint disease has been identified, but, as joint involvement is often limited, functional prognosis in AoSD seems to be less severe than in RA or other inflammatory arthritides [135].

6.8.2.3 Iatrogenicity

Corticosteroid side effects are also common because steroids are usually prescribed in high doses and the long term, which might contribute to the overall prognosis in AoSD.

6.9 AoSD Treatment

AoSD is rare, and no randomized controlled trial has been performed. Thus, the only information on therapy is from observational studies and retrospective case series. Recently, the management of AoSD benefited from the proofs of the efficacy of targeted biotherapies.

6.9.1 Symptomatic Treatments

Although NSAIDs, including aspirin, have been effective in systemic JIA, they are rarely effective in AoSD; only 20% of patients have achieved control with this therapy [1, 102, 103].

Of the NSAIDs, indometacin 150–250 mg/day seems to be the most effective [3, 102]. Liver enzymes must be monitored at the initial stages of the disease because severe hepatitis has been suggested to be related to treatment with NSAIDs [3, 102, 103].

Acetaminophen may help to reduce fever, although it is often not enough to suspend it. Other analgesics might be necessary to relieve intense myalgia and joint paint.

6.9.2 Corticosteroids

Once the diagnosis is established, corticosteroids are usually required to induce symptom remission. Optimal dosing relies on medium to high doses (i.e., 0.5–1 mg/kg/day of prednisone equivalent) [3, 5, 6, 16, 102]. Patients with serious visceral involvement might achieve a quick response with intravenous infusion of high-dose methylprednisolone [3, 102, 103]. Response to corticosteroids is often dramatic—within a couple of hours or a few days [3, 102].

The consensus is lacking on a therapeutic tapering scheme once clinical remission is achieved. However, owing to the potentially serious side effects of cumulative corticosteroid therapy, many others currently recommend to achieve the dose of 0.1 mg/kg/day after 6 weeks of therapy and to stop completely after three months. If this is not possible, the response should be considered inadequate, and a disease-modifying treatment, especially a targeted therapy, should be started (Fig. 6.6) [16].

6.9.3 Methotrexate

Methotrexate is used as an immunomodulatory agent in rheumatoid arthritis. It is efficient in controlling AoSD disease activity and allowing for steroid dose sparing [3, 136–138]. However, whether methotrexate can prevent or limit joint structural damage in the erosive form of AoSD, as has been shown for RA, is unclear. The presence of liver enzyme abnormalities does not contraindicate methotrexate prescription, but close biological monitoring is necessary [3, 102, 136, 137].

Of importance, methotrexate can be associated with anti-IL-1- or anti-IL-6-targeted therapies.

6.9.4 Targeted Therapies for AoSD

Different targeted therapies have been used to treat refractory AoSD (Table 6.5). The medical need is high, keeping in mind the unsatisfactory rates provided by

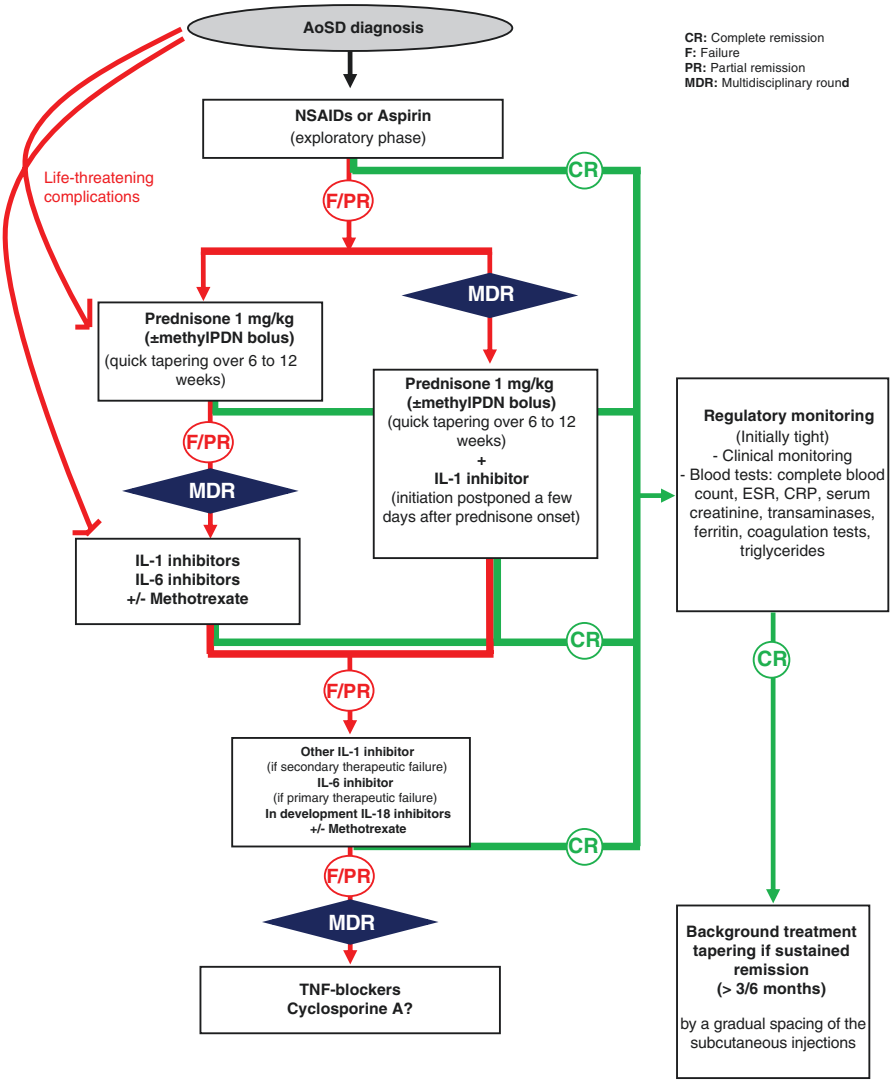

Fig. 6.6 Therapeutic strategies to manage AoSD patients. *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *IL* interleukin, *methylPDN* methylprednisolone, *NSAIDs* nonsteroidal anti-inflammatory drugs, *TNF* tumor necrosis factor

classical therapies with NSAIDs or conventional disease-modifying antirheumatic drugs (DMARDs). The use of glucocorticoids is also limited by the known long-term safety issues, especially with higher doses. In fact, for at least 30–40% of patients, the disease cannot be controlled by glucocorticoids even when combined with conventional DMARDs, such as methotrexate.

Table 6.5 AoSD targeted therapies

Targeted therapy	International nonproprietary name and usual dose	Reported no. of patients	Preferential AoSD pattern	Follow-up (months)	Complete remission (%)	Steroid dose reduction	References
IL-1 receptor antagonists	Anakinra 100 (sometimes 200) mg/day SC	>250	Systemic and articular	>12	80	Yes	[46, 68, 69, 139–144]
Anti-IL-1ß	Canakinumab 150 (sometimes 300) mg/month SC	<5	Systemic and articular	>12	100	Yes	[145–147]
IL-1 trap	Rilonacept Loading dose of 100–320 mg and then 100–320 mg/week	<5	Systemic and articular	>12	100	Yes	[148]
TNF blockers	Infliximab 3–7.5 mg/kg at W0–W2–W6 and then every 6–8 weeks IV Or Etanercept 50 mg/7 days SC	<100	Articular	>12	0–100	n.k.	[149–154]
IL-6 receptor antagonists	Tocilizumab 8 mg/kg/month IV Or 162 mg/week SC	<150	Systemic and articular	>12	60–85	Yes	[155–162]
Anti-IL-18	Tadekinig alfa 80 mg/week SC Or 160 mg/week SC	<25	NA	4	n.k.	n.k.	[163]
B cell directed	Rituximab 1 g D1–D15 every 6 months	Single case	NA	12	n.k.	n.k.	[164]
T cell directed	Abatacept 500–1000 mg/month IV[a] Or 125/week SC	Single case	NA	>12	n.k.	n.k.	[165, 166]

D day, *IV* intravenously, *SC* subcutaneously, *W* week, *NA* not available, *IL* interleukin, *TNF* tumor necrosis factor, *n.k.* not known

[a]Abatacept dose depends on patient's weight: <60 kg =500 mg, 60–100 kg = 750 mg, ≥100 kg = 1000 mg

6.9.4.1 IL-1 Inhibition

The use of IL-1 inhibitors for AoSD contributed to the revival of considering this mode of action in rheumatology and now represents the primary choice for treating autoinflammatory diseases in general. However, it took surprisingly long until clinical development moved forward from cohort studies to randomized, placebo-controlled trials. Currently, two IL-1 blocking compounds are the focus of phase 2/phase 3 studies with different designs.

Anakinra, a recombinant IL-1 receptor antagonist, was the first biologic showing beneficial effects in treating the systemic and articular features of AoSD in many case series, uncontrolled trials, and different national surveys. Although the evidence for its efficacy has not been proven by controlled trials, the overall number of more than 250 published cases provides convincing results. In fact, a clear and sustained improvement was described for systemic and also arthritic symptoms in most treated cases [68, 139–143]. Systemic features seem to show a more rapid response, and longer exposure seems usually required for improvement of arthritis. Of major importance for long-term safety were consistent reports of a reduction or even discontinuation of glucocorticoids use as well as NSAIDs. In this context, meta-analyses from eight case series and three national surveys meeting predefined quality standards and including more than 100 anakinra-treated AoSD patients revealed a remission rate of approximately 80% and a reduced use of steroids in approximately 35% of patients [69]. Recently, a large observational retrospective multicenter study from Italy added evidence for a strong impact on disease activity with the Pouchot score as well as clinical and serological features regardless of sex, age, disease pattern, or co-medication [46]. Since September 2017, a randomized, double-blind, placebo-controlled, multicenter, phase 3 study in the United States has recruited patients for investigating two different doses of anakinra (2 mg/kg/day [max 100 mg/day] or 4 mg/kg/day [max 200 mg/day]) to evaluate its efficacy and safety in patients newly diagnosed with SoJIA and AoSD. The primary end point, American College of Rheumatology 30 (ACR30) response, has already been evaluated at week 2; however, the overall treatment period is short, with only 12 weeks of exposure followed by a 4-week safety follow-up [167]. Of note, anakinra is the only IL-1 blocker for which we have substantial long-term results in terms of efficacy and safety in AoSD [144], and it has now been approved in this indication. In contrast to monogenic autoinflammatory diseases, in AoSD, remission can continue in some cases even after treatment is stopped. However, a relatively high withdrawal rate of 40% has been reported owing to loss of response over time and also to frequent injection site reactions to the required daily administrations.

The other approved biologic for AoSD is canakinumab, a fully human antibody against IL-1β [145]. Furthermore, canakinumab is also approved for treating other autoinflammatory diseases including cryopyrin-associated periodic syndromes, familial Mediterranean fever, TNF receptor-associated periodic syndrome, and hyper-IgD syndrome as well as SoJIA. Although the overall experience with canakinumab in AoSD is still limited, the reported response of systemic features and arthritis was rapid and sustained over many months to years in most patients, frequently allowing for tapering of steroids [145–147]. Of note, canakinumab was

found highly effective for patients with AoSD who were difficult to treat, including those showing failure of NSAIDs, glucocorticoids, and other IL-1 inhibitors. With these promising results, a placebo-controlled, randomized, multicenter, phase 2 study of canakinumab in AoSD is ongoing [168]. The dosage of canakinumab with monthly injections of up to 4 mg/kg body weight (maximum dos of 150 mg) is based on the pharmacokinetic profile in adolescent patients with SoJIA. The primary aim is to investigate the efficacy of canakinumab in patients with AoSD and active joint involvement in terms of the proportion of patients with a clinically significant reduction in disease activity (Disease Activity Score in 28 joints [DAS28] > 1.2) following a treatment period of 12 weeks. The overall placebo-controlled period is 24 weeks, but nonresponders can be unblinded and show treatment rescue at week 12. The core study is followed by an optional long-term extension over 2 years to provide additional safety results in the adult population.

In summary, the published data for anti-IL-1 agents in refractory AoSD clearly show a consistently high rate of full or partial remission with the additional achievement of lowering or stopping glucocorticoid medication [169].

6.9.4.2 IL-6 Inhibition

Inhibition of IL-6 signaling is possible by two different approaches, the direct neutralization of the cytokine or the blockade of the respective receptor. None of these mechanisms has been investigated in AoSD in a controlled setting of clinical trials in detail. For the two different IL-6 receptor antagonists currently available in daily practice for treating rheumatic diseases, only the tocilizumab AoSD case series has been published and reported at conferences [155–158]. To summarize, the observed anti-inflammatory effects were strong, rapid, and sustained for most of the cases. Usually, the systemic features disappeared entirely, but also the arthritic manifestations improved, and the serologic activity decreased [159, 160]. However, because of limited data, the likelihood of response cannot be estimated as clearly as for IL-1 inhibitors and seems to be between 60% to 80% in terms of full remission. A recently published meta-analysis of ten original studies (147 individuals) on the efficacy of tocilizumab and AoSD revealed overall high partial and complete remission rates of 85–77%, respectively. Tocilizumab prevented new flares, was well tolerated, and could significantly reduce the need for corticosteroids [161, 162].

Whether other IL-6 inhibitors have similar effects remains unknown. As shown for RA treatment, with AoSD, differences could exist with respect to safety, especially in comparison to the direct cytokine inhibitors. Also, the advantages or disadvantages that distinguish IL-6 and IL-1 inhibition are unclear. Although clearly IL-6 as well as IL-1 inhibitors have high response rates and represent alternative approaches in AoSD, we have no way to predict the individual effects and define the ideal treatment algorithm.

6.9.4.3 IL-18 Inhibition

A novel compound is Tadekinig alfa, a recombinant human IL-18 binding protein [163]. This drug was tested in healthy volunteers and patients with psoriasis and

RA in phase I studies and demonstrated a good safety and tolerability profile with only mild adverse events at the injection site. Because of the postulated role of IL-18 in the pathogenesis of AoSD, it was a logical step to investigate the effects of Tadekinig alfa in this condition. A first open-label, dose-finding phase 2 study involving multiple centers in Europe was designed to capture safety information as the primary outcome. Two doses (80 and 160 mg) were administered during 12 weeks, and patients were followed up for 4 more weeks. As a secondary outcome measurement, the efficacious dose at 3 weeks was defined as normalization of body temperature and decrease of CRP level by 50% or more of baseline values.

Although limited by the low patient number and short observation period in the study, the safety profile of Tadekinig alfa was overall acceptable, with injection site reactions and infections being the most frequent adverse events. In terms of efficacy, reduced level of CRP as well as other inflammatory markers (including IL-18, ferritin) was detected in some patients. Furthermore, an improvement in skin rash and a slight but significant reduction in the prednisolone doses were reported. In summary, inhibition of IL-18 by Tadekinig alfa could be a promising new approach in ASOD that needs to be investigated in a controlled setting.

6.9.5 Other Potential Agents with Less Validated Indication

Many other treatments have been tried in AoSD, with varying degrees of success.

6.9.5.1 TNF Inhibition

Stimulated by encouraging results from other chronic inflammatory joint diseases, especially RA, TNF inhibitors have been the first biologics used for AoSD [149–154]. However, driven by the deceptive impression that AoSD, with a predominant arthritic phenotype, is a subgroup of seronegative RA, the results from uncontrolled trials involving usually small cohorts of patients were inconsistent. Since favorable outcomes have been seen in only a few patients without any specific characteristics, TNF inhibitors can only be considered third-line drugs, preferentially for patients with chronic arthritis.

6.9.5.2 Cyclosporine A

Cyclosporine A has been proposed before the era of biotherapies, in patients with systemic features of AoSD or with RHL, with an interesting efficacy. However, the tolerance of this drug limits its use, but it certainly can be of interest in complex or refractory situations.

6.9.5.3 Intravenous Immunoglobulins

There is henceforth no place for intravenous immunoglobulins in AoSD treatment, owing to the efficacy of the other therapies available.

6.9.6 Treatment Strategies

The strategy we propose for AoSD patients is summarized in Fig. 6.6.

6.9.7 Treatment and Management of Life-Threatening Complications

6.9.7.1 Reactive Hemophagocytic Lymphohistiocytosis (RHL)

Management should include, firstly, symptomatic care in a medicine department or intensive care unit (ICU); secondly, active and rapid search for an infection; and, thirdly, introduction of high-dose steroids. Since RHL has described under IL-1 therapy, it appears prudent to introduce this treatment only after RHL control by a few days of high-dose steroids.

6.9.7.2 Coagulation Disorders

DIC is a medical emergency whose care combines:

1. Supportive measures, which could include platelet transfusion, coagulation factors (or fresh frozen plasma), and fibrinogen (in cryoprecipitate) infusion to control severe bleeding or sometimes heparin if no active bleeding is present [70].
2. Specific anti-inflammatory agents often decided in multidisciplinary rounds, with mainly high-dose corticosteroids, either intravenous (methylprednisolone 15 mg/kg/day) or oral (prednisone 1 mg/kg/day) [59]. To limit steroid exposure, the addition of other immunomodulatory agents, such as IL-1 or IL-6 blockers or cyclosporine, is recommended [68, 69, 71–73].

TMA treatment is complex and mandatorily includes [60]:

1. Supportive care in an ICU, with plasma exchange being central [75]
2. High-dose steroids intravenously and then orally

Other immunomodulatory agents proposed for refractory cases include anakinra [74], tocilizumab [76], intravenous immunoglobulins, cyclophosphamide, azathioprine, cyclosporine A, and rituximab [60, 74]. Despite this treatment, mortality associated with TMA remains high, up to 20% [60].

6.9.7.3 Cardiac and Pulmonary Involvements

Their treatment combines supportive care, high-dose steroids, and frequently IL-1 or IL-6 inhibitors.

Regarding PAH, early diagnosis is central for the prognosis of this complication, with mortality remaining as high as 40% [60]. The diagnosis includes [80, 82, 83, 85, 86, 100, 101]:

1. Hospitalization in an ICU and rapid referral to a specific reference center for multidisciplinary round discussions.

2. Vasodilating therapies frequently combining endothelin receptor antagonists (bosentan, ambrisentan), phosphodiesterase-5 inhibitors and other guanylate cyclase stimulators (sildenafil or others), and prostacyclin analogues.
3. High-dose steroids, initially intravenously and then orally.
4. Rapid introduction of biologic immunomodulatory agents targeting IL-1 or IL-6 or other immunosuppressive agents, such as methotrexate, azathioprine, cyclophosphamide, cyclosporine, or rituximab. However, these treatments must be carefully monitored because a few cases of PAH worsening have been described after their introduction.

PAH deserves to be well known by physicians caring for AoSD patients because it was not described in most of the initial AoSD case series for several reasons: now better diagnostic tools for PAH; differential efficacy of large-spectrum immunomodulatory agents, such as steroids, as compared with more targeted therapies, such as IL-1 or IL-6 blockers; and exposure to microorganisms as an additional target whose ecology may have evolved in recent years.

6.9.7.4 Amyloidosis

Even administered late, AoSD therapy, such as steroids and above all IL-1 and IL-6 blockers, may at least in part improve the clinical and biological symptoms.

6.10 Conclusion

In the last 15 years, substantial progress has been made in the diagnosis and prognosis of AoSD. The coming years will likely contribute to a better understanding of the disease and its complications, notably in disease pathogenesis, identification of diagnostic and prognostic biomarkers, and new targets for preventing both life-threatening manifestations and chronicity.

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Recurrent Pericarditis

7

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Abbreviations

AHA	Anti-heart antibodies
AIDA	Anti-intercalated-disk antibodies
AIRTRIP	The Anakinra-Treatment of Recurrent Idiopathic Pericarditis
ANAs	Antinuclear antibodies
AP-1	Activator protein-1
APC	Antigen-presenting cell
ASA	Acetylsalicylic acid
CEACAM1	Carcinoembryonic antigen cell adhesion molecule 1
CMR	Cardiac magnetic resonance
CMV	Cytomegalovirus
CRP	C-reactive protein
CT	Computerized tomography
DAMP	Damage-associated molecular patterns
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ESC	European Society of Cardiology
ESR	Erythrocyte sedimentation rate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigens
HSV-1	Herpes simplex virus

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IL	Interleukin
INF	Interferonγ
IRP	Idiopathic recurrent pericarditis
IVIg	Intravenous immunoglobulins
MHC	Major histocompatibility complex
MICA	MHC class I chain-related protein A
NF-kB	Nuclear factor-kappa B
NSAIDs	Nonsteroidal anti-inflammatory drugs
PAMP	Pathogen-associated molecular patterns
PPS	Postpericardiotomy syndrome
STIR	Short-tau inverted recovery
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TRAPS	TNF receptor–associated periodic fever syndrome

Chapter Overview

- Idiopathic recurrent pericarditis may have an autoinflammatory pathogenesis.
- Idiopathic recurrent pericarditis is a diagnosis of exclusion.
- Inflammatory markers and imaging can support the diagnosis and management.
- Interleukin-1 antagonists are effective in difficult-to-treat patients.

Pericarditis is an entity characterized by similar clinical pictures sustained by different pathways. The spectrum of possible causes is broad: in about 70% of children and more than 80% of adults, a specific etiology cannot be detected, and pericarditis is therefore labeled idiopathic [1, 2], even if the etiopathogenesis is suspected to be viral- or immune-mediated. Idiopathic forms typically have a good prognosis with often a full recovery within several weeks. However, pericarditis may recur in about 20–40% of the cases, and recurrences are the most challenging common management issue and a frequent reason of concern for both the physician and the patient. Recently, idiopathic recurrent pericarditis (IRP) has been considered to be sustained by an autoinflammatory pathway. The spectacular effect of the interleukin (IL)-1 receptor antagonist anakinra has reinforced this notion and has led to the consideration of a new pathogenetic mechanism [3, 4].

7.1 Definitions

The European Society of Cardiology (ESC) guidelines define acute pericarditis as an inflammatory pericardial syndrome with specific manifestations, including chest pain (85–90% of cases), typically sharp, improved by sitting up and leaning forward; pericardial friction rub (30% of cases); electrocardiogram (ECG) changes (60% of cases)—with new widespread ST elevation or PR depression or nonspecific repolarization abnormalities; and pericardial effusion (60% of cases in the first attack and

50% in the recurrences) assessed by echocardiography [2]. Confirmatory findings include elevation of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and the white blood cell count or evidence of pericardial inflammation with computerized tomographic (CT) scan or cardiac magnetic resonance (CMR) [2]. Recurrent pericarditis is defined as a relapse after a first acute episode followed by a symptom-free interval of at least 4 weeks, corresponding to the usual duration of anti-inflammatory therapy in noncomplicated cases [2]. Recurrent pericarditis Recurrent pericarditis

may be differentiated from *incessant* pericarditis, in which symptoms persist for more than 4–6 weeks but less than 3 months, and from *chronic* pericarditis, in which the symptoms last longer than 3 months [2].

7.2 Epidemiology

Limited data describe the incidence of IRP. Acute pericarditis is common. The incidence was 27.7 cases per 100,000 population per year in an Italian community [2], but a study from Denmark reported a higher incidence (168 cases per 100,000 population per year) [5]. The Italian paper evaluated only data from emergency rooms and hospital admissions, and the diagnosis was confirmed by the investigators, while the Danish study included also outpatients and pericardial effusions not due to acute pericarditis; this probably explains the observed discrepancy between the two studies. The rate of recurrences varied in studies between 20% and 30% after the first episode and between 20% and 50% after the first recurrence [2]. Recurrences may be related to an inadequate treatment of the previous attack. Familiarity has been reported in 10% of the patients with IRP [6].

7.3 Etiology

The etiology of pericarditis is heterogeneous. Several nonspecific triggers may activate the inflammatory cascade. Two major categories are recognized: infectious (viruses, mycobacteria, other bacteria) and noninfectious (neoplastic, autoimmune, traumatic, metabolic, iatrogenic, drug-related) [2]. In 70% of pediatric patients and more than 80% of adult patients, a definite etiology cannot be recognized, and pericarditis is therefore labeled idiopathic.

7.4 Pathogenesis

The pathogenesis of IRP is not known. Infectious (mainly viral), autoimmune, or autoinflammatory pathways have been suggested.

An infectious mechanism is proposed by molecular analysis on epicardial biopsies and pericardial fluid that identified a virus in approximately 20% of cases [1]. However, standard techniques are not diagnostic in the vast majority of cases. Recurrences may theoretically result from inability to clear the virus. This might explain the increased risk of relapse in patients treated with corticosteroids, even if

too rapid, corticosteroid tapering is often the more probable cause of most of these cases. Overall, antiviral therapy is usually not considered.

Some observations suggest an autoimmune pathogenesis: antinuclear antibodies (ANAs) [7] are present in about 40% of the patients with IRP as well as anti-heart and anti-intercalated-disk antibodies, in 50% and 25% of IRP patients, respectively [8]. Other supportive observations for an autoimmune mechanism include the presence of cytokines, such as interferon (INF)-γ, IL-8, and IL-6, in the pericardial fluid, and the association of IRP with human leukocyte antigen (HLA) DQB1∗0202A∗02, Cw∗07, and in a lower frequency DQB1∗0302 [9]. Moreover, pericarditis is common in systemic autoimmune disease, such as systemic lupus erythematosus (20–50% of patients), systemic sclerosis, rheumatoid arthritis, and Sjögren's syndrome, usually during a flare [1, 9]. Post-cardiac injury syndrome is sometimes considered a model of autoimmune pericarditis, triggered by damage to pericardium or blood in the pericardial space, due to open heart surgery or other invasive procedures or after myocardial infarction. The exposure of pericardial antigens may induce an autoimmune response activating B- and T lymphocytes [10]. On the other hand, an autoinflammatory pathogenesis may also be involved (production of massive amount of damage-associated molecular patterns [DAMP]).

ANAs may be positive in patients with IRP, even if generally at low titers (≤1/80); they are not specific and have low clinical significance [11], since they are equally positive in patients with recurrent pericarditis associated or not with a definite rheumatologic disease.

The last and more recent hypothesis suggests the involvement of the innate immune system. The demonstration of the spectacular effect of anakinra in refractory recurrent pericarditis was a sort of proof of concept [3, 4, 12]. Pericarditis may be observed in many monogenic autoinflammatory diseases such as familial Mediterranean fever, tumor necrosis factor (TNF) receptor–associated periodic fever syndrome (TRAPS), and Hyper IgD syndrome (mevalonate kinase deficiency) [13]. We published that 6% of IRP patients carried a mutation in the *TNFRSF1A* gene (in most cases, the nonspecific R92Q mutation) [14]. The spectacular effect of anakinra suggests a pivotal role for the inflammasome in the pathogenesis of this condition [15].

In conclusion, the initial trigger of pericarditis may be different, while the pathway that sustains the recurrences is autoinflammatory in nature, with a pivotal role for IL-1 (Fig. 7.1).

7.5 Clinical Manifestations

The almost universal symptom of pericarditis is chest pain, worsened by lying supine and improved by leaning forward; the patients recognize it as similar to previous attacks. In addition, at least one objective finding should be present (ECG changes, pericardial rub, and pericardial effusions) [2]. Symptoms are usually milder during recurrences, particularly when appropriate treatment is begun. In patients with a more intensely inflammatory phenotype fever, strikingly elevated

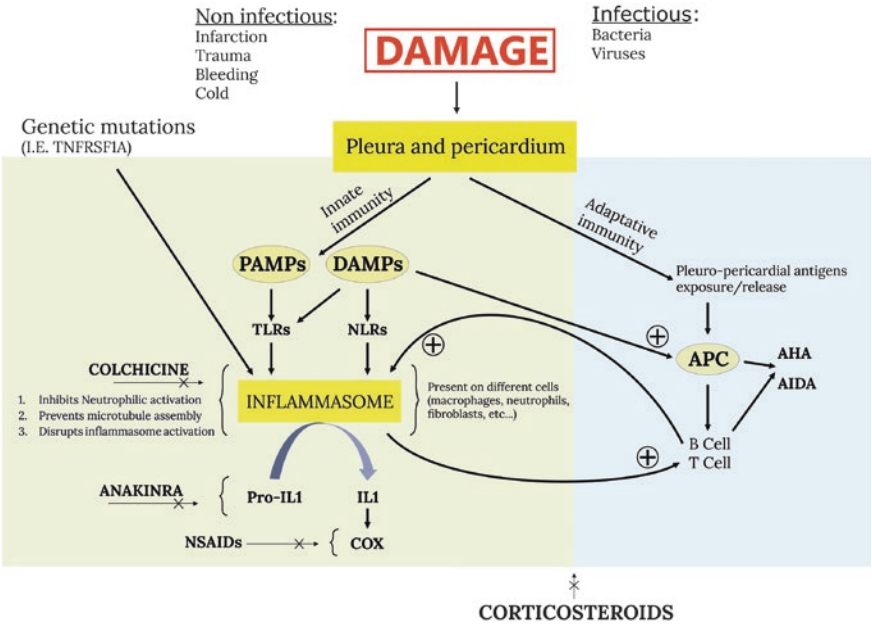

Fig. 7.1 General scheme of the supposed pathogenetic mechanisms of acute idiopathic recurrent pericarditis. *PAMP* pathogens-associated molecular patterns, *DAMPs* damage-associated molecular patterns, *TLR* toll-like receptors, *NLR* NOD-like receptors, *AHA* anti-heart antibodies, *AIDA* anti-intercalated-disk antibodies, *IL-1* interleukin-1, *NSAIDs* nonsteroidal anti-inflammatory drugs, *APC* antigen-presenting cells (from Ref. [16])

CRP, involvement of other serosal membranes (pleuropulmonary involvement in 55% of children, 36% of adults, and peritoneal involvement in 5%), and elevation of liver enzymes (8% in adult) can be recorded [17].

In the pediatric patients, the clinical picture is generally more inflammatory, with more common pleuropulmonary and systemic involvement. Accordingly, ANAs are less frequently positive in children. The autoinflammatory phenotype is clearer in children, with elevated CRP, fever, and pleural involvement [3, 18] (Table 7.1).

7.6 Laboratory Testing

There is no specific biomarker diagnostic for pericarditis. In the management of pericardial syndromes, a major controversy is the role of an extensive etiological search and admission for all patients with pericarditis or pericardial effusion [2]. The epidemiological background is essential to develop a rational cost-effective management program, and the clinician should especially identify causes that require targeted therapies. The diagnosis of "idiopathic cases" is essentially an exclusion diagnosis, supported by a typical clinical course. The ESC has proposed a diagnostic algorithm [2]. Auscultation, ECG, echocardiography, chest X-ray,

Table 7.1 Comparison of clinical features, etiologies, and outcomes in the largest published studies in pediatric (Raatikka, Imazio, Finetti) and adults (CORP2) patients with recurrent pericarditis

Feature	Raatikka [19] (*n* = 15 Children)	Imazio [18] (*n* = 110 Children)	Finetti [3] (*n* = 15 Children)	CORP2 [20] (*n* = 240 Adults)
Fever	12 (80%)	84 (76%)	8 (53%)	73 (30%)
Chest pain	15 (100%)	103 (93.6%)	13 (87%)	239 (100%)
Pericardial rub	n/a	31 (28%)	5 (33%)	82 (34%)
ECG	10/13 (77%)	49 (44%)	13 (87%)	25% [21]
Pericardial effusion	15 (100%)	86 (78%)	13 (87%)	138 (57%)
Elevated CRP	14 (93%)	102 (93%)	13 (87%)	174 (72%)
Tamponade	1 (7%)	15 (14%)	n/a	2 (1%)
No specific etiology	8 (53%)	98 (89%)	13 (87%)	198 (82%)
PPS	7 (47%)	10 (9%)	n/a	21 (9%)
ANA positivity	1 (*N* = 14) (7%)	18 (16%)	n/a	43% [7]
ASA/NSAIDs	4 (27%)	89 (81%)	13 (87%)	240 (100%)
Colchicine	4 (27%)	68 (62%)	14 (93%)	120 (50%)
Corticosteroids	11 (73%)	70 (65%)	15 (100%)	16 (7%)
Anakinra	0	12 (17.1%)	13 (87%)	0
Constriction (transient)	0 (0.0%)	3 (3%)	n/a	4 (7%)
Pleuropulmonary involvement	10 (67%)	54%	n/a	36% [17]
Liver involvement	n.a.	9 (8%)	n.a	8% [17]

CRP C-reactive protein, *ECG* electrocardiogram, *PPS* postpericardiotomy syndrome, *ANA* antinuclear antibodies, *NSAIDs* nonsteroidal anti-inflammatory drugs, *ASA* acetylsalicylic acid

routine blood tests—including markers of inflammation (i.e., CRP and/or ESR)—and myocardial lesion (troponins) are recommended in all cases of suspected pericarditis. Additional testing should be related to the suspected origin and clinical presentation. The major specific causes to be ruled out are bacterial pericarditis (especially tuberculosis), neoplastic pericarditis, and pericarditis associated with a systemic disease (generally an autoimmune disease). Each of these specific causes has a frequency of about 5% of all unselected cases of pericarditis from developed countries, while frequencies increase in moderate to large pericardial effusions [2]. Certain clinical features at presentation may be associated with an increased risk of specific etiologies (nonviral or nonidiopathic) and complications during follow-up (recurrences, tamponade, constriction), and are suggested as "high risk features" useful for the triage of pericarditis, to establish the need for a full etiological search, and admission in the single patient [2]. Factors indicated as "major" have been validated by multivariate analysis, while factors indicated as "minor" are based on experts opinion and literature review: they are essentially theoretical risk factors for complications and suggest the indication for admission and close monitoring of the evolution. Major risk factors include fever >38 °C (hazard ratio [HR], 3.56), subacute course (symptoms developing over several days or weeks; HR, 3.97), large pericardial effusion (diastolic echo-free space >20 mm in width) or cardiac

tamponade (HR, 2.15), and failure of aspirin or NSAIDs (HR, 2.50) [2]. Large effusion and tamponade (HR, 2.51) and aspirin or NSAIDs failure (HR, 5.50) also identify an increased risk of complications during follow-up (recurrences, constriction). Minor risk factors are pericarditis associated with myocarditis, immunodepression, trauma, and oral anticoagulant therapy.

For adult patients with predictors of poor prognosis, major or minor hospitalization and a full etiologic search are recommended by ESC [2]. On the contrary, when these negative predictors are absent, patients are at a low risk of specific causes and complications, and outpatient management may be considered. With a clear diagnosis of idiopathic origin and a recurrence course with complete symptom-free periods between the episodes, it is also unnecessary to repeat a new etiological search at each recurrence unless new clinical features become evident. Notably, viral serological tests are considered futile, since they have no impact on therapy and prognosis. Possible exceptions are those for human immunodeficiency virus (HIV) and hepatitis C virus (HCV). If a viral etiology is strongly suspected, generally in the first attack, a genome search with PCR is preferred for most viruses to serology, including cytomegalovirus (CMV), Epstein-Barr virus (EBV), parvovirus, adenovirus, and enteroviruses (echo and Coxsackie viruses), herpes simplex virus-1 and -2 (HSV 1 and 2) [2].

In case of a positive family history for pericarditis or periodic fever, genetic tests for monogenic syndromes may be considered [13, 14].

CRP and ESR are not specific but are important to guide the management of the disease [22]. A small study suggested that the carcinoembryonic antigen cell adhesion molecule 1 (CEACAM1) and the major histocompatibility complex (MHC) class I chain-related protein A (MICA) are possible biomarkers for IRP, but further investigations are warranted [23].

7.7 Imaging

Transthoracic echocardiography is the imaging modality of choice for the diagnosis of pericarditis [2]. It is a simple, low-cost, and noninvasive technique, easily performed at the bedside. It is safe and can be repeated without risks. It confirms the diagnosis by identifying a pericardial effusion and can demonstrate complications such as ventricular dysfunction, tamponade, constriction, etc. On the other hand, echocardiography hyperechogenicity or increased thickness of the pericardium are often limited by artifacts and are not specific.

CMR is a second-level technique that may be helpful to study pericardium and myocardium [2, 24]. On T1-weighted imaging, the normal pericardium appears like a thin hypo-intense (“dark”) curvilinear structure surrounded by hyper-intense (“bright”) epicardial and mediastinal fat. CMR may assess pericardial thickness (normal value < 4 mm) and edema. Pericardial edema appears bright on T2-weighted short-tau inverted recovery (STIR) fast spin-echo sequences. The tissue edema is not well delineated if there is a concomitant effusion, which appears as bright as the edema. Following intravenous paramagnetic gadolinium, enhancement may

demonstrate inflammation into the surrounding epicardial fat, which suggests severe inflammation. CMR is useful also in assessing myocardial edema, and fibrosis. It may also suggest evolving constrictive pericarditis. CMR is indicated also in patients in whom the presence of active pericardial inflammation is uncertain: delayed pericardial enhancement at CMR may favor continued or intensified anti-inflammatory treatment. On the other hand, if CMR does not show delayed pericardial enhancement, then tapering of medications may continue, and other diagnoses may be considered. CMR has some disadvantages, such as its limited availability and costs, and also the need of breath-holding and regular heart rhythms to get good picture quality. Contraindications include claustrophobia, pacemakers, and renal insufficiency.

CT scanning is a complementary imaging technique. It is important to evaluate presence of calcifications and anatomic features [2, 25]. The normal pericardium appears as a thin curvilinear structure surrounded by the hypodense mediastinal and epicardial fat on CT. CT can assess localized effusions, may quantify the amount of fluid and can give information about the nature of the effusion depending on attenuation values of fluid (HU). Low attenuation values (e.g., 0–20 HU) indicate a transudate, intermediate values (e.g., 20–60 HU) suggest exudative effusions, while high attenuation values (>60 HU) indicate hemorrhage. Intravenous administration of iodinated contrast may detect pericardial inflammation because of the enhancement of the inflamed pericardium after contrast injection. CT is generally considered mandatory in the preoperative work-up before pericardiectomy, to assess calcification and the anatomy of the pericardium. It is also very important to exclude important etiologies, such as neoplastic disease or tuberculosis [25].

7.8 Treatment

The treatment of patients with recurrences is not very different form the treatment of a first episode of acute pericarditis. Aspirin or NSAIDs remain the mainstay of therapy. Colchicine is recommended on top of standard anti-inflammatory therapy in order to improve remission rates and prevent recurrences. In case of incomplete response to NSAIDs and colchicine, corticosteroids may be used, but they should be added at low-to-moderate doses [2] (Tables 7.2 and 7.3).

7.9 Aspirin and Nonsteroidal Anti-inflammatory Drugs

Aspirin and NSAIDs remain the mainstay of treatment [2]. The specific drug selected is not important: the choice should be based on the physician's experience as well as on the history of efficacy and tolerability in the single patient. An NSAID that was effective in a previous attack should be the favorite drug of choice. Ibuprofen and aspirin are the most used. Indomethacin is perhaps the most powerful. Comorbidities are also important: for example, aspirin is generally not used in children, but it is the favored choice in patients with ischemic heart disease or when

Table 7.2 Nonsteroidal anti-inflammatory drugs and aspirin in the treatment of pericarditis: recommended regimens in adults

Drug	Dose	Length of Treatment	Tapering
Ibuprofen	600–800 mg every 8 h	First attack: 2–6 weeks Recurrences: several weeks to months The optimal length of treatment is debatable, and CRP should probably be used as a marker of disease activity to guide management and treatment length. Gradual tapering (every 2–4 weeks and only if the patient is asymptomatic and CRP is normal), is recommended	Decrease the total daily dose by 200–400 mg every 2–4 weeks
Aspirin	500–1000 mg every 6–8 h		Decrease the total daily dose by 250–500 mg every 2–4 weeks
Indomethacin	25–50 mg every 8 h		Decrease the total daily dose by 25 mg every 2–4 weeks
Naproxen	250–500 mg every 12 h; maximal daily dose 1500 mg for limited time period (<6 months). Dosage expressed as naproxen base; 200 mg naproxen base is equivalent to 220 mg naproxen sodium		Decrease the total daily dose by 125–250 mg every 1–2 weeks

The dosage ranges are based on weight, age, severity of the attack, and subjective tolerability
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Guidelines/Pericardial-Diseases-Guidelines-on-the-Diagnosis-and-Management-of v1.4
According to local availability of the different agents, we recommend intravenous use of NSAIDs in hospitalized symptomatic patients. Start at the lower end of dosing range and titrate upward
Renal impairment dosing: CrCl <30 mL/min: NSAIDs use is not recommended (for aspirin: use is not recommended if CrCl <10 mL/min)
Hepatic impairment dosing: use with caution; dose adjustment may be required [2]
CRP C-reactive protein, *NSAIDs* nonsteroidal anti-inflammatory drugs
Geriatric dosing: Refer to adult dosing. Use lowest recommended dose and frequency

a patient is already on aspirin or needs antiplatelet treatment. Naproxen is an alternative. Indomethacin and other NSAIDs should be avoided in patients with coronary artery disease.

During an acute attack, a practical tip in a hospitalized patient is the administration of aspirin or NSAIDs intravenously, above all, if the patient has intensive pain, high fever with associated nausea, or vomiting. Particular attention should be paid in using the highest well-tolerated dose of each medication and to obtain a continuous anti-inflammatory coverage throughout the day. A common mistake is to use too low doses. Aspirin should be used at the dose of 1.5–4 g/day; ibuprofen at 1200–3200 mg/day; and indomethacin at 75–150 mg/day (Table 7.2). The administration

Table 7.3 Nonsteroidal anti-inflammatory drugs: recommended doses in children with pericarditis

Drug	Dose	Length of Treatment and Tapering
Ibuprofen	30–50 mg/kg/24 h divided every 8 h	First attack: 2–6 weeks. Recurrences: several weeks to months The optimal length of treatment is debatable, and CRP should probably be used as a marker of disease activity to guide management and treatment length. A gradual tapering (every 2–4 weeks and only if the patient is asymptomatic and CRP is normal) should be considered
Indomethacin	Children ≥2 years: oral: 1–2 mg/kg/day in 3–4 divided doses; maximum dose: 4 mg/kg/day; not to exceed 150–200 mg/day	
Naproxen	Children >2 years: oral suspension is recommended: 10 mg/kg/day in two divided doses (up to 20 mg/kg/day if tolerated)	

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Guidelines/Pericardial-Diseases-Guidelines-on-the-Diagnosis-and-Management-of v1.4
Aspirin is generally considered contraindicated in children due to the associated risk of Reye's syndrome and hepatotoxicity
Start at the lower end of dosing range and titrate upward
CRP C-reactive protein

of NSAIDs should be well distributed during the day. For example, with regard to aspirin, ibuprofen, or indomethacin, each dose should be taken precisely in order to guarantee a full 24-h coverage [2].

7.10 Colchicine

Colchicine is recommended to be used in weight-adjusted doses (i.e., 0.5 mg once daily if body weight is <70 kg or 0.5 mg twice daily if it is ≥70 kg, for ≥6 months) in adults, to improve remission rates and prevent recurrences [2, 21]; similar approach is to start with 0.5 mg once daily and then, if tolerated, increase the dose to 0.5 mg twice daily or 1 mg daily, depending on compliance and tolerability. A loading dose is no more used, to avoid side effects and related early discontinuation. In children with IRP, frequently used doses are 0.5 mg/day *in children younger than* 5 years and 1–1.5 mg/day in older children [2]. Side effects are gastrointestinal (up to 10% of cases), including nausea, vomiting, diarrhea, and abdominal pain, usually being a common cause of drug withdrawal; generally mild, they may resolve with dose reduction. The duration of therapy is at least 6 months, but, if recurrences are frequent and colchicine is well tolerated, the duration can reach some years. At this point, discontinuation is discussed with the patient, and we prefer to taper it slowly.

7.11 Corticosteroids

Only after the use of high dosages of NSAIDs, corticosteroids may be added to aspirin/NSAIDs and colchicine as a triple therapy in cases of incomplete clinical control of the disease, particularly in adults, but at low to moderate doses (i.e., prednisone 0.2–0.5 mg/kg/day in adults) [2].

Corticosteroids block transcription factors such as nuclear factor-kappa B (NF-kB) and activator protein-1 (AP-1) which are involved in the transcription of many inflammatory mediators.

Although corticosteroids provide rapid control of symptoms, they favor chronicity, more recurrences, and side effects [2, 17, 18, 20, 24]. If corticosteroids are used, their tapering should be particularly slow. A critical threshold for recurrences is a 10–15 mg/day dose of prednisone or equivalent. At this threshold, very slow decrements as small as 1.0–2.5 mg at intervals of 2–6 weeks are useful. In cases of recurrence, every effort should be made not to increase the dose or to reinstate corticosteroids [2].

Corticosteroids should be used only in selected patients with specific indications (i.e., impending cardiac tamponade, pregnancy, systemic inflammatory diseases, some patients with postpericardiotomy syndromes), intolerance or resistance to standard therapy, and NSAID contraindications (renal insufficiency, true allergy, high risk of bleeding) [2]. Every decrease in corticosteroid dose should be done only if the patient is asymptomatic and CRP is normal. Calcium intake (supplement plus oral intake) of 1200–1500 mg/day and vitamin D supplementation of 800–1000 IU/day should be offered to all adult patients receiving glucocorticoids. Moreover, bisphosphonates are recommended to prevent bone loss in all men $\geq$ 50 years and postmenopausal women in whom long-term treatment with glucocorticoids is initiated at a dose $\geq$ 5.0–7.5 mg/day of prednisone or equivalent.

The increased risk of recurrences in patients treated with corticosteroids may well be due to too rapid tapering, not driven by symptoms and CRP values. Long-term corticosteroid use is particularly worrisome in pediatric patients due to their multiple side-effects, including growth impairment.

7.12 Tapering

After obtaining a complete response, tapering should be done with a single class of drug at a time, and finally, colchicine is gradually discontinued (over several months in the most difficult cases). Recurrences are possible after discontinuation of each drug. Each tapering should be attempted only if symptoms are absent and CRP is normal. For these reasons, the length of therapy may extend for months or even years in the more difficult cases.

7.13 Immunotherapy and IL-1 Inhibition

Immunotherapy is an alternative approach to treat refractory IRP [2]. Three drugs have been proposed: azathioprine, intravenous immunoglobulins (IVIg), and anakinra.

Azathioprine has been used in case reports or case series of adults and one retrospective cohort study [26].

IVIgs have been used in two small case series and one retrospective analysis describing only 14 cases [2]. IVIgs can be used as a corticosteroid-sparing agents and have a rapid onset of action; however, they are rarely used, probably due to the high cost and lack of good evidence.

Anakinra is a recombinant IL-1 receptor antagonist; it inhibits the action of IL-1. The IL-1 intracellular signaling pathway is involved in the prostaglandin release by macrophages and in chemotaxis of monocytes, lymphocytes, and polymorphonuclear leukocytes, in the activation of T cells, and in the stimulation of metalloproteinases. Anakinra was initially registered for the treatment of rheumatoid arthritis, but it has found its niche in the treatment of several rare autoinflammatory diseases. Its spectacular effect in IRP was first recognized in the pediatric population [3, 18], and this was a proof of concept. Other case reports, cohort studies, one retrospective analysis, and a meta-analysis confirmed these findings. Finally, a double-blind randomized controlled trial (AIRTRIP-The Anakinra-Treatment of Recurrent Idiopathic Pericarditis) formally demonstrated the efficacy of anakinra in 21 patients with corticosteroid-dependent and colchicine-resistant recurrent pericarditis with elevated CRP [4]. Anakinra obtained quick symptom relief in a few days and allowed steroid discontinuation in all patients within 6 weeks. It was administered as a once daily subcutaneous injection at the dose of 100 mg in adults (1–2 mg/kg/day in children) for 6 months [4]. Recurrences can occur if tapering is too rapid. Tapering regimes are not established, and it is very difficult to propose a universal tapering regimen (as it would very difficult to propose a similar tapering regimen for corticosteroids for instance). A possible scheme might be to withdraw a dose every month after a full control of the disease has been reached: for example, first step, 100 mg/day, every day for 6 months; second step, in the 7th month, 100 mg/day, six times per week; third step, 100 mg/day, five times per week for 1 month, and so on until the seventh step, 100 mg once per week, in the 14th month. A critical point for recurrence might be at the dose of two doses weekly. A similar approach would be the following: when the patient reaches the three dose/weekly regimen, the following tapering may be done not considering the week but considering the interval between two consecutive doses, for instance, one dose every third day, then every fourth day, and so on.

The drug is generally well tolerated. The most common adverse events are skin reactions at the site of injection, neutropenia, and mild elevation of transaminases.

In children, anakinra might now be considered prior to corticosteroids, to avoid their side effects in the growing child. There are only few case reports on the use of other anti-IL1 antagonists such as canakinumab in IRP [27].

7.14 Outcome and Prognosis

Severe complications are rare in IRP [2]. Cardiac tamponade is uncommon and usually occurs at the beginning of the disease. A small risk to evolve in constrictive pericarditis exists after the first episode of acute pericarditis (less than 1%) [28], but on the other hand, constrictive pericarditis has never been reported in IRP, in spite of numerous recurrences [17, 29]. Thus, it is important to reassure patients about their prognosis, explaining the likely course and the nature of the disease. Drug treatment should take into account this favorable outcome to avoid iatrogenic damages, particularly due to corticosteroids, particularly in the pediatric patients. However, the quality of life can be severely impaired due to repeated recurrences, frequent hospitalizations, and corticosteroid dependence [2]. IRP may last for years if not properly treated. IL-1-inhibitors have proved to be quick and highly efficient, also in refractory cases, and their role is becoming more prominent. In our experience, most patients continue treatment with anakinra for 1–3 years, at low doses. At present, approximately 40% have discontinued treatment. In case of recurrence during anakinra tapering, NSAIDs may be useful to control mild recurrences [4].

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Chronic Nonbacterial Osteomyelitis

8

Andrea Taddio and Serena Pastore

8.1 Introduction

Chronic nonbacterial osteomyelitis (CNO is a rare inflammatory disorder (OMIM 259680) not related to infectious diseases that affect children and adolescents and more frequently females than males (4:1) [1]. It was first described in 1972 by Giedion et al. [2] as unusual symmetric multifocal bone lesions due to sub-acute or chronic osteomyelitis. Later, in 1980, Bjorksten and Boquist [3] first used the term CNO. Its hallmark is recurring episodes of sterile osteomyelitis [4–9].

Multiple names are used in the literature to describe this disorder; these include chronic recurrent multifocal osteomyelitis (CRMO) in cases with extended multifocal involvement (often symmetric) and synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome (SAPHO), which usually manifests in adolescent and adult patients. In the pediatric literature, the terms CRMO and CNO are often used interchangeably and will be used as such in this chapter. It is still unclear if SAPHO and CNO are different diseases presenting in different age groups or if they represent the spectrum of the same disease.

Although CNO is still considered a rare disorder with a prevalence between 1/160,000 and 1/2,000,000 and an incidence between 1/250,000 and 1/1,000,000, the disease is probably underestimated.

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8.2 Pathogenesis

The etiology of CNO is still unclear. The hypothesis of a disorder sustained by infections was not confirmed by extensive microbiological analyses. Bacterial cultures from the lesions are negative as well as the search for pathogens from the blood or joint fluids [10]. Moreover, antibiotics do not alter the course of disease [4]. Some authors classified CNO as a variant of juvenile spondyloarthropathy [5] because of its association with sacroiliitis [6] and Crohn's disease [7]; however, the detection rate of HLA-B27 [8] was inconsistent, and the distinctive clinical features, characterized by the presence of aseptic osteomyelitis, do not fit with spondyloarthropathies. Recent findings indicate that an imbalance between pro- (IL-6 and TNF-a) and anti-inflammatory (IL-10) cytokines may be centrally involved in the molecular pathogenesis of CNO [4]. Another study has recently demonstrated increased IL-1β secretion by peripheral blood mononuclear cells of CNO patients during active disease and expression of inflammasome components by CNO [11].

In the past few years, the hypothesis that CNO might be a genetic disease in the spectrum of autoinflammatory disorders has acquired even more importance. The strongest evidence comes from the so-called syndromic forms of CNO such as Majeed syndrome, Cherubism, and primary hypertrophic osteoarthropathy (PHO).

Majeed syndrome is the most known and the first disease associated with CNO. It is characterized by recurrent episodes of fever and is associated with congenital dyserythropoietic anemia and a febrile neutrophilic dermatosis, characterized by the onset of painful erythematous-violaceous lesions (Sweet syndrome–like) [12]. Majeed syndrome results from mutations in the LPIN2 gene. This gene provides instructions for synthesizing a protein called lipin-2. This protein seems to play a role in the processing of fatty acids at different levels. However, no lipid abnormalities have been found in Majeed syndrome. Lipin-2 also may be involved in controlling inflammation and in cell division. It is unclear how these genetic changes lead to bone disease, anemia, and inflammation of the skin [13]. Cherubism is a rare, benign, dominantly inherited, non-neoplastic bone disease. It is characterized by bilateral bone enlargement of the jaw in childhood leading to a full round face and an upward cast of the eyes in patients. The disease is related to the mutation in the gene *SH3BP2* in chromosome 4p16.3 [14]. Primary hypertrophic osteoarthropathy also known as pachydermoperiostosis and Touraine–Solente–Golé syndrome, is a very rare disease characterized by the presence of pachydermia, digital clubbing, and periostosis. Its pathogenesis involves genes related to prostaglandin E2 metabolism. Cases have been reported with an autosomal recessive inheritance pattern, with pathogenic variants in *HPGD* and *SCLCO2A1* genes responsible for pachydermoperiostosis types 1 and 2, respectively [15].

In addition, chronic osteomyelitis is a typical feature of two monogenic diseases caused by mutations of genes involved in the activation of the NLRP3 inflammasome or in the homeostasis of IL-1, namely pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome [16] and deficiency of IL-1 receptor antagonist (DIRA) [17], respectively.

There is also some evidence for a genetic basis in nonsyndromic or sporadic CNO. Golla et al. [18] reported a susceptibility locus on human chromosome 18q21.3–18q22 in a small German CNO cohort.

Moreover, in large cohorts of CNO patients, the prevalence of the disease among patients' relatives varied between 12% and 32% [19]. Several reports have described families with multiple affected members [20] or have reported a high incidence of psoriasis, inflammatory bowel disease, and other chronic inflammatory conditions in first-degree family members of individuals with CNO, which suggests that there is a significant genetic component to disease susceptibility [3, 5, 18]. Additional evidence of a possible genetic contribution to disease comes from studying the role of interleukin-10 in disease pathogenesis. One small study reported the association of CNO with polymorphism of the IL-10 promoter, and functional data suggest that IL-10 deregulation may play a role in disease pathogenesis [21]. Recently, it has been demonstrated that impaired MAPK signaling, reducing H3S10 phosphorylation, and Sp1 recruitment to the IL10 promoter, may lead to an impaired gene expression confirming a role of IL-10 [22].

It is also interesting to underline that murine models of the disease have also been described. Homozygous mutation of the *pstpip2* gene in mice results in an autoinflammatory disease very similar to CNO [23, 24]. Other candidate genes including *PSTPIP1*, *FBLIM1*, *CARD15/NOD2*, and *IL1RN* have been analyzed in small CNO cohorts [6, 7, 25, 26] with negative results.

Finally, it has been demonstrated that intestinal microbiota of diseased *pstpip2* mice was characterized by an outgrowth of Prevotella. *Pstpip2* mice that were fed with a diet rich in fat and cholesterol maintained a normal body weight but were markedly protected against inflammatory bone disease and bone erosions; diet-induced protection against osteomyelitis was accompanied by marked reductions in intestinal Prevotella levels and significantly reduced pro-IL-1β expression in distant neutrophils. Furthermore, pro-IL-1β expression was also decreased in *pstpip2* mice treated with antibiotics and in wild-type mice that were kept under germ-free conditions, suggesting that diet-associated changes in the intestinal microbiome could be a crucial factor in regulating inflammasome [27].

8.3 Clinical Manifestations

The clinical manifestations of CNO are highly variable. CNO typically presents with bone pain that is worse at night and can occur in the presence or absence of fever [6, 7, 28]. The onset is typically insidious, and most children appear well.

Swelling and warmth of the involved bone are not necessarily always present. In 30% of cases, CNO involves the adjacent joint with the presence of exudate, synovial thickening, and/or damage to the articular cartilage. The lesions may affect any bone segment. One to 20 sites can be affected at one time. The main sites of involvement in the order of decreasing frequency are the lower extremities, pelvis, clavicle, and spine [1, 6–8]. Involvement of clavicle, mandible, and sternum is particularly suggestive of CNO [9]. The skull involvement has been described in the occipital

bone in only one case. In this patient, however, the lesion was not present at the time of diagnosis but developed after 1 year from diagnosis [29].

Systemic symptoms are subtle and may be present in the form of low-grade fever, malaise, or poor growth. Current estimates suggest that approximately 25% of individuals with CNO have manifestations involving organ/systems other than bone [8]. The extra-articular manifestations include the skin (especially psoriasis, palmoplantar pustulosis, acne, pyoderma gangrenosum, and Sweet syndrome) and the bowel (Crohn's disease, ulcerative colitis, and celiac disease) [6]. Renal involvement has been demonstrated in almost 10% of patients (personal data). The combination of synovitis, acne, palmoplantar pustulosis, hyperostosis, and osteitis configures the SAPHO syndrome and, as reported above, seems to be the most severe form of CNO with, in particular, systemic clinical features.

The disease may follow a chronic or recurrent disease course, but often, the course is prolonged over several years with periodic exacerbations [1–6, 10]. The prognosis is generally good and provides self-resolution in a time ranging from months to years. However, recently variable complications from mild to incapacitating have been described in a considerable percentage of cases (30–50%). In particular, asymmetries of limb length, kyphosis, chronic spondyloarthropathy, vertebral collapse, and stunted growth for early closure of the growth of cartilage have been reported [6, 8, 9].

Monophasic disease is usually less severe, and prognosis is excellent, being, in most cases, almost a cosmetic problem.

8.4 Diagnosis

CNO is a diagnosis of exclusion [8, 19, 30]. Differential diagnoses include infections (septic osteomyelitis, typical and atypical mycobacterial infections, etc.), malignancies (primary bone tumors and leukemia/lymphoma), benign bone tumors (osteoid osteoma), trauma, metabolic disorders (including hypophosphatasia), other autoinflammatory disorders (DIRA, PAPA, Cherubism, etc.), osteonecrosis, and osteopetrosis. Laboratory investigations may reveal mild elevation in white blood cell count and in inflammatory parameters (C-reactive protein; erythrocyte sedimentation rate), but often, these abnormalities are absent in CNO patients [8, 19, 30]. Cultures of blood and bone are invariably negative, and sophisticated assays to identify evidence of a microbial etiology have been unsuccessful. Autoantibodies (antinuclear antibodies and rheumatoid factor), as well as carriage of the HLAB27 allele, have the same prevalence in CNO patients as in healthy individuals. At present, no specific biomarkers are available for the diagnosis or prediction of flares in CNO patients. In 2007, Jansson et al. [8] proposed diagnostic criteria for CNO according to which diagnosis could be formulated in the presence of two major and one minor criteria or one major and three minor criteria. Major criteria are the following: radiologic osteolytic/sclerotic bone lesion, multifocal bone lesions, palmo plantar pustulosis or psoriasis, and sterile bone biopsy with signs of inflammation, sclerosis, and/or fibrosis. Minor criteria are normal blood count and general

well-being, CRP and ESR mild to moderate and elevated, observation longer than 6 months, hyperostosis, association of other autoimmune diseases and first- or second-degree relatives with autoimmune or autoinflammatory disease or with CNO. However, these criteria are not still validated and accepted so far. A crucial role in the diagnosis of this condition is provided by imaging.

8.4.1 The Role of Radiology

Standard radiography of bones could not reveal characteristic changes in early CNO, while the presence of osteolytic lesions with a sclerotic edge on X-ray imaging is the key feature later. Clavicular and mandibular lesions often have a more prominent sclerotic appearance [31].

Cortical bone is usually unaffected and thickened, but there are also reports of cortical defects mimicking tumor; the involvement of the mandible is often associated with mandibular nerve canal enlargement (Fig. 8.1). Since CNO is a systemic disorder that can affect multiple skeletal sites, whole-body imaging techniques provide major contribution to the initial diagnostic approach, as well as during follow-up. Isotopic bone scan and/or whole-body magnetic resonance (MR) is the cornerstone for confirming the multifocal pattern of CNO. However, if bone scan may just confirm the presence of one or more foci of inflammation, MRI may also add more information concerning the type of lesions being the more sensitive and accurate radiological test for CNO diagnosis (Fig. 8.2). It also avoids the administration of radiations as for the case of traditional radiology, scintigraphy, or computerized tomography (CT). Similar to the X-ray technique, the typical findings at MR

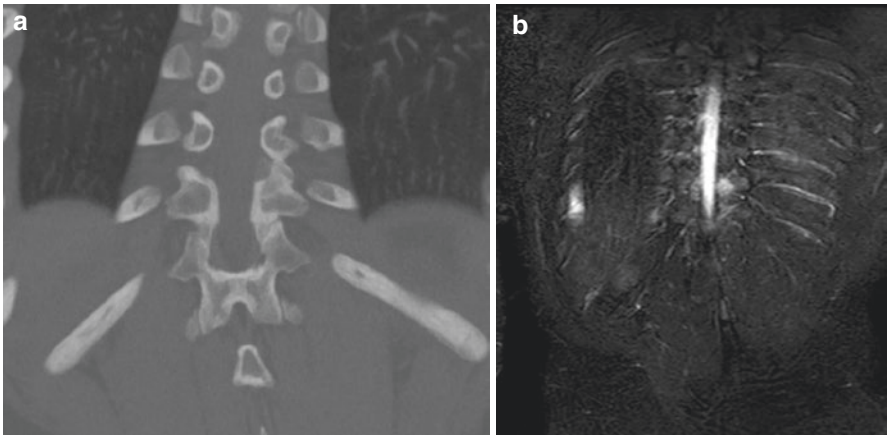

Fig. 8.1 (**a**) Spine CT. Coronal plane reconstruction. Well-defined lytic lesion of left inferior articular facet of T10, without clear signs of reactive sclerosis. The inferior articular facet of T9 appears normal. (**b**) Spine MRI. STIR sequence (Short-Time Inversion Recovery) in the coronal plane. Focal area of hyperintensity of the left T9–T10 facet joint, for bone marrow edema, without thecal sac compression signs

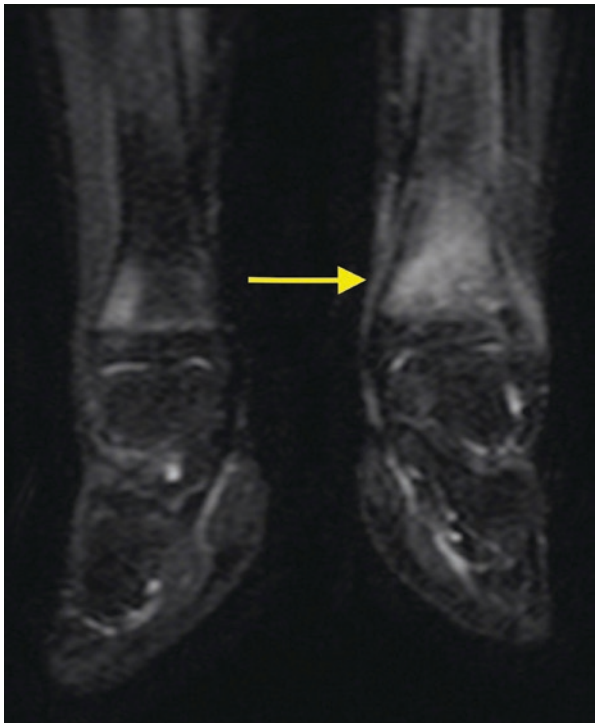

Fig. 8.2 Ankle section of T2-STIR whole-body MRI of a patient with CRMO. The arrow shows hyperintensity of bone with edema of soft tissues. The patient presented a clinical involvement of both mandible and ankle

are the presence of bone cortical thickening, lytic lesions with sclerosis, and bone edema. Moreover, MR is particularly important in the early stages of the disease for its ability to detect bone edema and asymptomatic bone lesions [32] before osteolysis and/or sclerosis can be detected, and it is useful for the identification of lesions at multiple sites. On the other hand, it should be mentioned that, due to its high sensitivity, this technique might lead to an over-interpretation of some bone lesions that, especially in pediatric age, can be related to normal bone growth or accidental traumatic events. This issue should be taken into careful consideration if the site of the bone biopsy is chosen on the basis of the MR images.

Due to the lack of ionizing radiation, whole-body MRI (with STIR sequences) is currently used to monitor the evolution of the bone lesions during the follow-up. Again, due to its high sensitivity, MRI might provide signs of possible bone activity in a subgroup of patients who do not complain of any clinical manifestation or bone pain and could be considered in clinical remission [33]. For this reason, it is not clear if the evidence of radiological disease activity in spite of a persistent clinical and laboratory remission should be taken into consideration for treatment decisions. For this reason, serial MRI scan can be useful in particular among patients with a more severe disease course and resistant to ongoing treatments, and in case of the involvement of some specific sites, such as the mandible or the spine, which is traditionally characterized by a higher rate of complications such as scoliosis or kyphosis.

8.4.2 The Role of Biopsy

Although no formal guidelines are so far available, a biopsy of the bone lesion is usually performed, mainly to exclude other causes. In CNO, bone biopsy shows signs of inflammation in the absence of infection. The composition of cellular infiltrates at the sites of inflammation is strictly correlated to the "age" of biopsied lesions. Neutrophils are predominant in early lesions, whereas lymphocytes, macrophages, and plasma cells can be detected during the later course of the inflammatory process.

Immunohistochemistry studies show T CD8+ cells, CD3+ and CD45RO+, CD20+ B cells, and CD68+ macrophages [3]. The final stage of the lesion is characterized by the predominance of fibrosis. The cultures of the biopsy are always negative [7].

Although histological findings are nonspecific, the main role of the biopsy is to rule out malignancy such as histiocytosis, Ewing sarcoma, osteosarcoma, and lymphoma. All these disorders should be considered in the differential diagnosis of persistent bone pain in all age groups.

A young female with migratory large joint polyarthralgias and bone pain, mimicking CNO, who finally received the diagnosis of T-cell rich B-cell lymphoma has been reported [34]. Primary lymphoma of the bone (PLB) is rare, comprising 5% of all primary malignant bone tumors and 2% of all extranodal non-Hodgkin's lymphomas. The diagnosis of PLB requires a bone lesion with unequivocal histological evidence of lymphoma. Unfortunately, there are no PLB pathognomonic radiographic findings; however, in this case, the clinical picture was characterized by a relapsing/remitting bone pain, which is not typical of CNO, and by the presence of skull involvement, which, as already said, is not classically associated with the disease.

Recently, [8] have proposed a clinical score that could facilitate the diagnosis and treatment process, particularly with respect to the decision on whether to carry out invasive procedures required for the diagnosis of these diseases [8]. The clinical score, derived using quantitative statistical techniques, includes many of the factors previously associated with diagnosis, such as the number, location, and symmetry of radiologically proven lesions; the presence of marginal sclerosis; body temperature; blood cell count; and CRP level. Using this tool, CNO was not probable with a clinical score of 0–28, uncertain (positive predictive value of 80%) with a clinical score of 29–38, and probable (positive predictive value of 97%) with a clinical score equal to or greater than 39. In the study by Wipff et al. [19], which applies this tool, biopsies would have been avoided for 27 out of 110 patients.

In conclusion, there is not a general agreement on the usefulness of biopsy for the diagnosis. Even if the Jansson Score is not still widely validated, it is suggested that patients with a score >39 may not undergo biopsy. Our practical approach is to perform a biopsy in all patients with poor general conditions, persistent and significant elevation of acute phase reactants, and/or hematological abnormalities (anemia, alteration in leukocyte or platelet counts) and in all those patients with unifocal or atypical (i.e., skull) bone involvement. On the contrary,

the decision to perform a biopsy can be postponed in patients in general good conditions, with slight elevation of acute phase reactants, involvement of multiple and/or typical bone sites, typical radiological findings and favorable response to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). In any case, further studies are needed to clarify the role of biopsy; up to now, the decision to perform a biopsy remains a physician-related decision based on his expertise and knowledge of CNO diagnosis.

8.5 Treatment

No guidelines exist on CRMO treatment, and most evidence comes from small case series or retrospective cohorts. No randomized clinical trial on CRMO treatment has been published until now. The drugs used are summarized in Table 8.1.

Table 8.1 Most common treatment options used in chronic recurrent multifocal osteomyelitis patients

	Dosage	Time of treatment
First-line treatment		
NSAIDs (nonsteroidal anti-inflammatory drugs)		
– Ibuprofen	30–40 mg/kg/die in three to four divided doses	1–3 months
– Indomethacin	1–2 mg/kg twice daily	1–3 months
– Naproxen	5–7.5 mg/kg twice daily	1–3 months
– Diclofenac	2–3 mg/kg in three divided doses	1–3 months
Corticosteroids		
– Prednisolone	1–2 mg/kg once daily	15–30 days then tapering
Second-line treatment		
Sulfasalazine	10–15 mg/kg four times daily	1–3 months
Methotrexate	15–20 mg/msq once weekly s.c.	6 months
Bisphosphonates		
– Pamidronate	1–3 mg/kg/day for 3 consecutive days every 3 months[a]	9 months
	or	
	1 mg/kg/day for 1 day every month	6 months
Anti-TNFα		
– Infliximab	5 mg/kg/dose. Infusions at time 0, 2 weeks, 6 weeks, then every 8 weeks	12 months
– Etanercept	0.8 mg/kg/dose/week	6 months
– Adalimumab	24 mg/mcq/2 weeks	6 months

Time of treatment is intended as the minimum time to treat the patients, but therapy can be prolonged according to clinical status

Table from Ref. [35]

[a]First infusion: 0.5 mg/kg

8.5.1 NSAIDs

The first-line treatment is considered to be nonsteroidal anti-inflammatory drugs (NSAIDs), with reported good response in small case series [36], even if clinical remission is not always achieved.

Their main role is pain control, but they may also prevent bone damage being involved in prostaglandin control [32]. Studies have demonstrated that the rate of clinical remission with NSAIDs is variable, ranging from 27% [37] to 80% [15, 29]. Their mechanism of action is mostly due to an anti-inflammatory effect on the bone; however, it is not clear which NSAIDs should be considered the best treatment option, and most NSAIDs are used interchangeably. The most commonly used NSAIDs for CRMO are ibuprofen, diclofenac [38], indomethacin [39], and naproxen.

The only NSAID evaluated prospectively is naproxen. In a study on 37 CRMO patients, a good response was shown in 43% of cases at 1 year of follow-up; improvement was demonstrated clinically as well as radiologically and with improved quality of life as well [40].

NSAID action starts after at least 4 weeks of therapy, so it is important to maintain the treatment for at least 1 month before declaring a failure [38].

8.5.2 Corticosteroids

Corticosteroids are the most effective anti-inflammatory drugs; their effects are mediated either by direct binding of the glucocorticoid/glucocorticoid receptor complex to glucocorticoid responsive elements in the promoter region of genes or by an interaction of this complex with other transcription factors, in particular activating protein-1 or nuclear factor-kappa B. These drugs inhibit many inflammation-associated molecules such as cytokines, chemokines, arachidonic acid metabolites, and adhesion molecules [41].

Oral corticosteroids have been proposed for those patients with CRMO who failed to respond to NSAIDs, as well as a first-line treatment choice, with a very good response rate [42]. The most used corticosteroid preparation is prednisolone.

8.5.3 Sulfasalazine and Methotrexate

Sulfasalazine is usually used in patients with associated inflammatory bowel disease but has not been reported to work better than NSAIDs.

Methotrexate (MTX) is a well-known treatment for rheumatologic conditions, especially in juvenile idiopathic arthritis. The drug inhibits purine and pyrimidine synthesis, accounting for its efficacy in the therapy of cancer, but many studies have focused on the adenosine-mediated anti-inflammatory effects of methotrexate as well. MTX has also been used in CRMO; however, in this clinical setting, it does not seem to be very effective [43]. In a cohort of 70 children with CRMO [44], only 20% of patients treated with MTX had clinical remission.

For those patients who do not respond to first-line treatment, bisphosphonate and/or TNF-α blockers have been used with variable effects.

8.5.4 Bisphosphonates

Although it is not clear how bisphosphonates exert their anti-inflammatory effect, it has been suggested that they may modify the release of proinflammatory cytokines acting on local effector cells, such as resident macrophages, osteoclasts, and fibroblasts [45].

Bisphosphonates have been used in CRMO since 2001 with good clinical effects and durable response [46]. Later, Simm and Miettunen treated five and nine CRMO patients, respectively, with bisphosphonate infusions, which led to pain decrease, symptomatic improvement, and radiologic improvement of bone lesions [47, 48]. Even though it is still unclear which subset of patients could benefit more from bisphosphonate treatment, studies suggest that they are more effective in those patients with multifocal lesions [15], spinal involvement [49], and, interestingly, mandible involvement [50]. Pamidronate is the most used bisphosphonate, but neridronate has been demonstrated to be effective as well [51]. A randomized trial on the use of pamidronate in CRMO patients is ongoing, and results are not yet available (NCT02594878).

In our and others' opinion, bisphosphonates should be used in patients when NSAIDs and corticosteroids have failed if no systemic feature is present and possibly as first-line treatment in those patients with spine involvement [10, 52, 53].

8.5.5 TNF Inhibitors

TNF-α is considered a key protein in inflammation, and its blockade is used in many autoinflammatory and autoimmune disorders. Moreover, TNF has been implicated in pathological bone resorption, activating osteoblasts and tissue stromal cells to express receptor activator of NF-kB (RANK) ligand (RANKL). In addition, TNF can act directly on osteoclast precursors, often in synergy with RANKL, to promote osteoclastogenesis [54].

Anti-TNF-α agents have been used in CRMO patients. Infliximab was the first biologic used [55], but etanercept and adalimumab have also been demonstrated to be effective [56, 57]. Their use has usually been for those patients, usually <10%, who did not achieve clinical remission with previous treatment. In these patients, benefit was observed [15]. In our opinion, TNF-α blockers should be considered when bisphosphonates failed, or as an alternative when systemic features (e.g., fever) are present.

8.5.6 Anti-IL1β

In consideration of the fact that CRMO is considered an autoinflammatory disease, some authors suggest that IL1 blockade could be a useful therapeutic approach also

for those patients with the sporadic form of CNO other than in those with inflammatory osteitis secondary to autoinflammatory syndromes [58].

Recently, three consensus treatment plans (CTPs) have been developed for the first 12 months of therapy for CNO patients refractory to NSAID monotherapy and/or with active spinal lesions. The three CTPs are methotrexate or sulfasalazine, tumor necrosis factor inhibitors with optional methotrexate, and bisphosphonates. Short courses of glucocorticoids and continuation of NSAIDs are permitted for all regimens. Consensus was achieved on these CTPs among CARRA members [59].

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Behçet Disease

9

Erdal Sag, Yelda Bilginer, and Seza Ozen

9.1 Behçet Disease

Behçet disease (BD) is a vasculitis that can affect arteries or veins of any size; thus, it was recently reclassified as a variable vessel vasculitis. BD is characterized by recurrent oral and/or genital ulcers accompanied by ocular, cutaneous, articular, gastrointestinal, and/or central nervous system inflammatory lesions [1]. Hulusi Behçet, a Turkish dermatologist, had described three major signs (oral aphthae, genital ulcerations, and uveitis) of BD in 1937 and defined it as a "triple symptom complex" [2]. There are also reports about BD description in the fifth century BC in the "*Third Book of Endemic Diseases* [3]."

9.2 Classification

Definition of Behçet disease is based on clinical features. As it shares overlap features with other autoinflammatory diseases, a number of classification criteria have been proposed. The main purpose of these classification criteria is to reach some uniformity. However, the heterogeneity of the disease poses problems, and it may be difficult to apply them to children.

Several sets of diagnostic criteria have been proposed so far. The most widely used diagnostic criteria for adults is the criteria of the International Study Group (ISG) (Table 9.1) with a specificity of 96% and sensitivity of 91% [4]. Recently, a large cohort of pediatric BD patients from both European and non-European countries was evaluated, and the first classification criteria of pediatric BD—PEDBD—(Table 9.2) was proposed with a sensitivity of 77% and specificity of 88% [5]. A multicenter study comparing PEDBD and ISG criteria with 68 pediatric BD patients

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Table 9.1 Criteria of the International Study Group for the diagnosis of Behçet disease [4]

Criterion	Description
Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration recurring at least three times in one 12-month period, observed by physician or patient
Plus two of the following:	
Recurrent genital ulcers	Aphthous ulceration or scarring observed by physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, or cells in vitreous on slit-lamp examination or retinal vasculitis observed by an ophthalmologist
Skin lesions	Erythema nodosum observed by physician or patient; pseudofolliculitis or papulopustular lesions; and acneiform nodules observed by physician in postadolescent patient not on corticosteroids
Pathergy	Erythema nodosum observed by physician or patient; pseudofolliculitis or papulopustular lesions; and acneiform nodules observed by physician in postadolescent patient not on corticosteroids

From Criteria for diagnosis of Behçet disease. International Study Group for Behçet disease. Lancet, 1990. 335(8697): p. 1078–80

Table 9.2 PEDBD pediatric Behçet classification [5]

Item	Description
Recurrent oral aphthosis	At least three attacks/year
Genital ulceration or aphthosis	Typically with scar
Ocular involvement	Anterior uveitis, posterior uveitis, and retinal vasculitis
Skin involvement	Necrotic folliculitis, acneiform lesions, and erythema nodosum
Vascular signs	Venous thrombosis, arterial thrombosis, and arterial aneurysm
Neurological signs	With the exception of isolated headaches

Three of six items are required to classify a patient as having pediatric BD (all having the same value)
From Kone-Paut, I., et al., Consensus classification criteria for pediatric Behçet disease from a prospective observational cohort: PEDBD. Ann Rheum Dis, 2016. 75(6): p. 958–64

and 90 controls also supports that PEDBD had a higher sensitivity (73.5% vs. 52.9%) but slightly lower specificity (97.7% vs. 100%) than ISG criteria [6].

9.3 Epidemiology

Behçet disease is very common in countries located along the "silk route" from the Far East to the Mediterranean basin. As a result, the highest prevalence has been reported in Northern China, Iran, Korea, and Turkey [7–9]. In Turkey, the overall prevalence is 1 in 250 persons [10]. The countries with the lowest prevalence are the UK, Portugal, Sweden, and the United States [11]. The usual age of onset is around 30 years. The prevalence of BD among children is low, and it has been proposed that it is not more than ten cases per 100,000 in Turkey [12]. The mean age at diagnosis is 7.8 ± 4.3 years in the International PEDBD cohort study of 156 patients [5].

9.4 Etiology and Pathogenesis

The pathogenesis of BD is still not clear. BD is an inflammatory disease where both the innate immune system and possibly the adaptive immune system are involved.

There is evidence supporting the genetic influence in the pathogenesis of BD. The frequency of familial cases is reported to be as high as 10–50% [13, 14]. The human leukocyte antigen HLA-B*5101 has the strongest genetic association with BD [15]. Besides HLA-B51, other HLA class I alleles such A26, B15, B27, and B56 represent independent risk factors for BD [16]. Recent genome-wide association studies have identified nearly 20 loci, most of which are involved in both innate and acquired immune systems. Among them, interleukin (IL)-10, IL-23 receptor, C-C chemokine receptor 1, and IL-12 receptor beta genes have been proposed as candidate genes involved in the pathogenesis [16–19]. Furthermore, the Mediterranean fever gene (MEFV) and Toll-like receptor (TLR)-4 have been found to be associated with BD, suggesting the role of innate immune responses against bacterial components in the pathogenesis of the disease [20]. Epigenetic influences are particularly important in the pathogenesis as studies point to DNA methylation and microRNAs altering TH17 cells [21, 22].

The genetic findings provide new insights into the pathogenesis of the disease. The HLA-B51 gene, which is a major histocompatibility complex (MHC) class I allele, was shown to have an epistatic interaction with endoplasmic reticulum aminopeptidase 1 (ERAP1) [23]. It has been shown that a hypoactive ERAP-1 allotype contributes to Behçet disease risk by altering the peptides available for binding to HLA-B51 [24]. ERAP-1 is a molecule in the endoplasmic reticulum that prepares peptides to effector cells by MHC class I molecules [23]. Polymorphisms in ERAP-1 have also been reported in ankylosing spondylitis or psoriatic arthritis. Altered preparation of peptides by ERAP-1 variants might play a role in the disease pathogenesis [25, 26]. On the other hand, a growing number of studies have reported that Th-17-associated cytokines are found in increased volumes in BS, emphasizing the role of IL-17/IL-23 axis and hence the adaptive immune system in the pathogenesis of the disease [27, 28].

On the other hand, BD has also been classified as a polygenic autoinflammatory disease because of the clinical features, the role of the innate immune system in the inflammatory process, and the recurrent nature of the disease. Although microbial agents have been proposed as a causative factor in the disease pathogenesis, thus far, no single pathogen has emerged a likely candidate [29]. Although microbial studies have shown distinct oral or intestinal microbiota, whether the changes in microbiota are a causative factor or a consequence of this condition is not clear [30, 31].

Haploinsufficiency of A20 may mimic Behçet disease. Thus, mutations in the relevant genes should be sought for if the medical history suggests inherited disease with early-onset systemic inflammation [32].

9.5 Clinical Manifestations

The clinical presentation of BD is quite heterogeneous: features may differ among different regions over the world. In Far East, gastrointestinal disease is seen more

frequently, while in the Eastern Mediterranean region and Middle East, vascular involvement is more common. Pathergy positivity and HLA-B51 carrier rate are also more frequently encountered in the countries on Silk Road than in the United States and Europe [33].

The course of the disease is characterized by exacerbations and remissions, with a more severe course in the first years after diagnosis. Skin and mucocutaneous symptoms are the most common and usually are the presenting manifestations, while vascular, neurological, and eye involvement are less common but are associated with morbidity and even mortality. It is not easy to diagnose BD in childhood, as the major manifestations that are needed to classify BD may not be seen at disease onset. The mean interval between the initial and the second major manifestations was 2.9 years, while the third and the fourth features may develop more rapidly [5, 34].

9.5.1 Fever

Recurrent fever is not a common finding in the adult BD cohorts (22%), but it correlates with vascular, neurological, and joint involvement [35]. In the largest pediatric BD cohort, recurrent fever was seen in 44% of patients, without any significant association with other major manifestations [5].

9.5.2 Mucocutaneous Lesions

Oral ulceration is the most frequently seen (present nearly in all patients) and usually the presenting symptom (81%) in pediatric BD [5]. Oral ulcers in BD resemble recurrent aphthous stomatitis; however, they tend to be multiple, extremely painful, and more frequent (Fig. 9.1). Mucosal ulcers are generally located at the lip, tongue, palate, and anywhere in the gastrointestinal tract. They tend to last around 7–10 days (major ulcers may heal over weeks), recur at different intervals during the disease course, and totally recover without scarring. As they are very painful, they cause difficulty in eating, speaking, and even swallowing and interfere with the quality of life. Oral ulcers are generally the only manifestation in pediatric BD for a long time before the next manifestation appears.

Genital ulcers are painful recurrent ulcers, usually located at vulva and vagina in females and at glans penis and scrotum in males. They are seen in nearly 55–83% of the patients with a female predominance and heal with scarring. [5, 36] They are deeper and larger than oral ulcers and tend to have an irregular margin [37].

Other skin manifestations are also frequently seen in pediatric BD [38]. Typical skin lesions include erythema nodosum (more common in females), folliculitis, acneiform (papulopustular) lesions (more common in males), skin nodules, and ulcers [5]. These lesions generally appear after oral ulcers [5]. The skin of BD patients is sensitive to trauma and puncture. This skin hypersensitivity, pathergy, is a cutaneous pustular reaction occurring 24–48 h after a 24-G needle puncture. It is a highly specific but not pathognomonic feature of the disease.

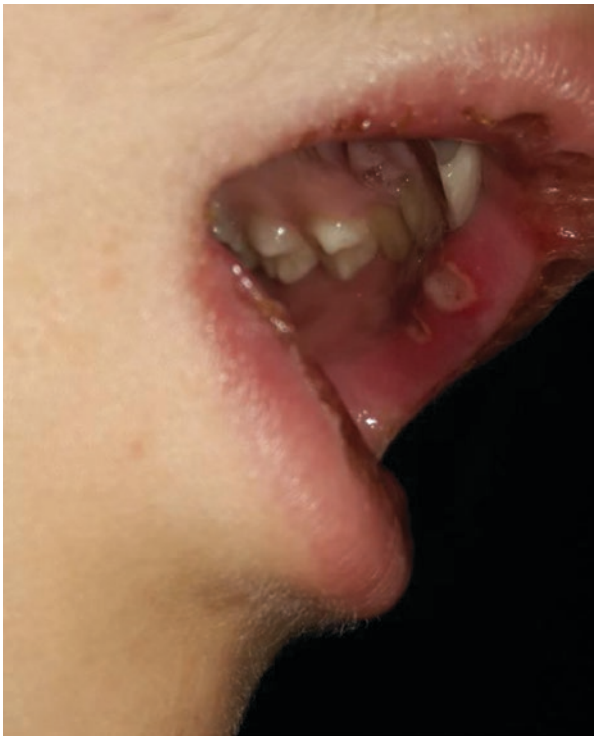

Fig. 9.1 Oral aphthous lesion in a girl with Behçet disease

Pathergy positivity was formerly a diagnostic criterion; however, it varies from 40% to 80% of the patients; thus, it is not a criterion in newly formed PEDBD classification criteria [5, 36].

9.5.3 Eye Involvement

Ocular lesions occur in about 30–45% of pediatric BD patients [5, 39]. The ocular disease may start unilaterally; however, the typical involvement is recurrent bilateral uveitis, which is characteristically nongranulomatous and affects anterior, posterior, or both segments [40]. Anterior uveitis is more common before 10 years of age, while bilateral panuveitis with retinal vasculitis and/or retinitis is the most common form of the ocular disease in patients older than 10 years [41]. In the latter form, patients tend to have a painless decrease in the visual acuity [37]. In anterior uveitis, blurred vision, redness, periorbital or global pain, and photophobia can be seen [40]. Hypopyon may also occur, and severe uveitis can cause loss of vision [40]. Complications such as posterior synechia, cystoid macular edema, glaucoma, and cataract may occur [40, 42]. Other rare ocular manifestations are corneal ulcerations, retinal detachment, and optic nerve involvement. Ocular disease is reported to be more serious and more frequent in males [5, 43].

9.5.4 Vascular Involvement

BD is classified as variable vessel vasculitis in the latest Chapel Hill Consensus Conference (CHCC) 2012 criteria [1]. It is a very peculiar disease affecting any size and any type (arterial and venous system) of vessel. BD is characterized by arterial or venous thrombosis and aneurysms or occlusions of the arterial systems. The main pathogenetic mechanism is the inflammation of the vessel wall leading to thrombus formation. Activated neutrophils produce excessive superoxide radicals and lysosomal enzymes that damage the vessel wall [42]. Endothelial damage with aneurysm formation causes local blood flow abnormalities. The thrombus is usually adherent and does not generate secondary embolism [42].

Vascular involvement is seen in 10–20% of BD patients, generally occurs about 3–5 years after the disease onset, and is more common among males [5, 36, 44]. Superficial or deep thrombophlebitis (generally of the lower extremities) and Budd-Chiari syndrome are the most common vascular manifestations in adults, while venous thrombosis of the lower extremities and cerebral sinus thrombosis are the most common vascular disease in children [29, 44–47]. Arterial complications including aneurysm and thrombosis may also occur [47], as well as pulmonary and central retinal artery involvement [48–50]. Although rare, pulmonary artery aneurysm/thrombosis is a very severe form of vascular BD, presenting with dyspnea, hemoptysis, and chest pain [51, 52]. Pulmonary artery aneurysms, typically involving main pulmonary arteries and their lobar branches in a young man, are almost exclusively due to BD [53]. Among 47 patients with pulmonary arterial involvement, peripheral venous thrombosis (77%) was also present [52]. In a study of 21 pediatric BD patients with thrombosis, four had anticardiolipin antibodies and two had Protein C deficiency, suggesting that the presence of thrombophilic markers could increase the risk of thrombosis in BD [45].

9.5.5 Neuro-Behçet

Neurological involvement is one of the most severe causes of long-term morbidity and mortality in BD [54]. Central nervous system involvement occurs in 5–10% of patients [55]. The frequency of neurological involvement in children ranges from 15% to 30% [5]. Central nervous system is the major target of neurological involvement. The two major forms of neurological involvement in BD are parenchymal and nonparenchymal involvement [56].

- *Parenchymal involvement*: Subacute meningoencephalitis occurs in 75% of cases. Onset is commonly subacute, and headache is common before and during attacks [56]. Different presentations can be seen.
  - Brain stem involvement: ophthalmoparesis, cranial neuropathy, and cerebellar or pyramidal dysfunction
  - Cerebral hemispheric involvement: encephalopathy, hemiparesis, hemisensory loss, seizures, dysphasia, and mental changes (cognitive dysfunction and psychosis)

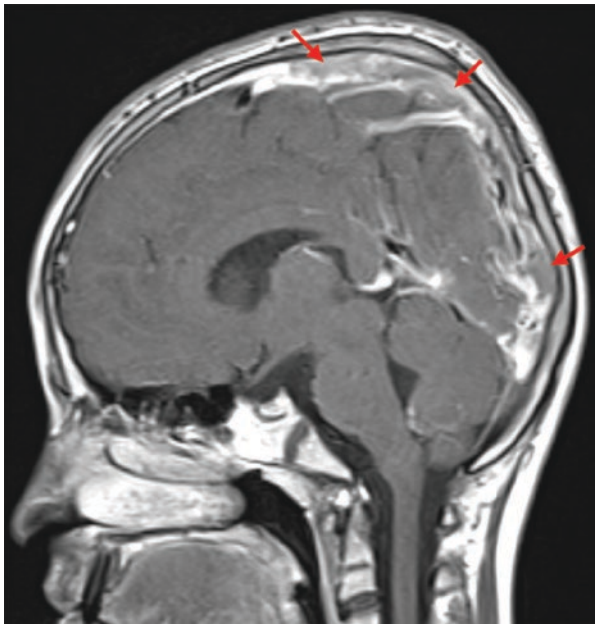

Fig. 9.2 Dural sinus thrombosis (red arrows)

  - Spinal cord involvement: pyramidal signs in the limbs, sensory-level dysfunction, sphincter dysfunction [56]
- *Nonparenchymal involvement*: Main structures of the central nervous system are involved. The nature and severity of the clinical syndrome depend on the structure involved.
  - Cerebral venous sinus thrombosis (Fig. 9.2) occurs in 10–20% of BD patients with neurological involvement [54]. Clinical onset is subacute or chronic in most patients. Patients present with severe headache, mental changes, and motor ocular cranial nerve palsies (sixth or less often third cranial nerve) [57]
  - Intracranial aneurysms
  - Extracranial aneurysms/dissection

Peripheral nervous system involvement, psychiatric symptoms, and optic neuropathy are seldom observed [54].

The main manifestations in the pediatric age group is cerebral venous thrombosis and cranial nerve palsy (especially sixth) rather than parenchymal lesions [42].

9.5.6 Musculoskeletal Involvement

Poly- or oligoarthritis is seen in nearly half of pediatric BD patients [5, 36]. It generally affects knees, elbows, ankles, and wrists; however, any joint can be involved. Recurrent nonerosive peripheral arthritis (47%) is the most common involvement,

but axial arthritis (16%) and, very rarely, HLA-B27-related spondyloarthropathy (2%) can also occur [5].

Besides arthritis, acute localized myositis has been reported in a very few pediatric BD patients [58].

9.5.7 Gastrointestinal Involvement

Gastrointestinal (GI) involvement in BD is very challenging due to the similarities to inflammatory bowel diseases (IBDs). It is more frequent in Japan and France, with a more severe course [33]. Abdominal pain (26–41%) and diarrhea (13%) are the most common symptoms. Although very rare, there may be ulcers (5–15%), bleeding (2–5%), and perforation (1–2%) [5, 44, 46]. Ulcers in BD are round/oval; usually deep, large, and single; mostly located in the ileocecal region; and very fragile with a tendency to perforate [59]. Chronic active inflammation, crypt distortion, and, rarely, vasculitis can be seen in the biopsies taken from these ulcers [59]. In 20% of patients, the ulcers relapse even with appropriate treatment [59]. GI involvement has a more severe course in juvenile-onset BD patients [59].

9.5.8 Renal Involvement

Kidney involvement is relatively more frequent than has been recognized, but it is generally mild in nature. Glomerulonephritis (most commonly as crescentic GN and IgA nephropathy) and secondary amyloidosis are the most common features, while renal artery aneurysm, renal vein thrombosis, and, very rarely, tubulointerstitial lesions may also be seen [60].

9.5.9 Other Organ Involvements

Pulmonary artery involvement is the primary pulmonary involvement; however, parenchymal lesions (nodules and cavities), pleural effusions, and mediastinal lymphadenopathy have also been reported [52]. Cardiac complications (6–7%) include pericarditis, endocardial lesions (aortic regurgitation and, less often, mitral insufficiency), myocardial lesions (myocardial infarction, myocarditis, and endomyocardial fibrosis), and intracardiac thrombosis (right ventricle and atrium) [61, 62].

9.6 Diagnosis

There is no specific laboratory test to diagnose Behçet disease. Autoantibodies are not expected to be present. Acute-phase reactants are increased with active disease.

The histopathology of the pathergy test shows mixed inflammatory cell infiltration, endothelial swelling and thickening, erythrocyte extravasation, perivascular

cell infiltration, lymphocytic vascular reaction, lymphocytic vasculitis, and leukocytoclastic vasculitis [63].

Inflammation in the synovium is usually nonspecific. Synovial fluid analysis is characterized by a predominance of neutrophils and low glucose [64]. Metabolomic evaluation of Behçet arthritis revealed increased oxidative stress, providing a potential link to BD-associated neutrophil hyperactivity [65].

HLA-B51/B5 carriage predominates in males and is associated with moderately higher prevalence of genital ulcers and ocular and skin manifestations and a decreased prevalence of gastrointestinal involvement [66]. Although it is not a diagnostic criterion, the strength of the association between BD and HLA-B51/B5 and its consistency across populations of various ethnicities further support that this allele is a primary and causal risk determinant for BD [67].

9.7 Differential Diagnosis

The differential diagnosis is usually challenging and depends on the main clinical manifestation. Oral ulcers can be seen in recurrent aphthous stomatitis or a number of other diseases; however, ulcers in Behçet disease are more painful, usually multiple, and more frequent.

Gastrointestinal involvement should be differentiated from inflammatory bowel disease (IBD). Bowel lesions of Behçet disease are usually located in the ileocecal region and tend to be single, large, and deep; however, the differentiation is very challenging.

Thrombotic manifestations including sinus thrombosis or any type of arterial and venous thrombosis can be seen in diseases with genetic predisposition to thrombosis.

BD mimics all vasculitides, as it can affect any type of vessel, but the involvement of venous system inflammation is quite specific for BD.

9.8 Treatment

Treatment of BD depends on the site and severity of specific organ-system involvements. There are no controlled studies for the treatment of pediatric BD patients; thus, the treatment strategies mostly rely on studies in adults. Very recently, the new European League Against Rheumatism (EULAR) recommendations for adult BD have been proposed [68].

9.8.1 Mucocutaneous Lesions

Topical treatments like corticosteroids are generally used as the first-line treatment for oral and genital ulcers. Colchicine can be used to prevent recurrent oral and genital ulcers. Papulopustular or acne-like lesions are treated in a similar approach

used in acne vulgaris [68]. If the mucocutaneous lesions recur despite colchicine treatment, other immunomodulatory agents such as azathioprine, thalidomide, dapsone, interferon-alpha, and anti-tumor necrosis alpha (anti-TNF) agents can be used [69–73]. Apremilast, an oral phosphodiesterase-4 inhibitor, has been suggested as a promising agent for active mucocutaneous lesions and had very good results in a recent adult phase 2 trial [74].

Interleukin-1 (IL-1) blockade with anakinra and canakinumab and IL-23 blockade with ustekinumab provide partial benefit, while IL-17 blockade with secukinumab was ineffective and IL-6 blockade with tocilizumab worsened the mucocutaneous lesions [75–78].

9.8.2 Eye Involvement

Eye involvement should be managed with an experienced ophthalmologist. Isolated anterior uveitis can be treated with topical steroids, while systemic immunomodulatory agents such as azathioprine should be used in patients with poor prognostic factors such as young age, male gender, and early disease onset. Any BD patient with posterior eye involvement should be treated with azathioprine, cyclosporine A, interferon-alpha, or anti-TNF agents (infliximab or adalimumab). Systemic corticosteroids can also be added to these drugs [68]. During an acute attack, high-dose systemic corticosteroids, anti-TNF agents, or interferon-alpha can be used. In patients with unilateral exacerbation, intravitreal corticosteroid injection may also be added [68]. In an open-label randomized controlled trial (RCT), the IL-1-beta antibody gevokizumab reduced uveitis severity, decreased macular edema, and preserved visual acuity but did not affect the risk of ocular exacerbations [79]. There are also a few case series that show beneficial effect of tocilizumab in patients refractory to azathioprine, interferon-alpha, and anti-TNF agents [80, 81].

9.8.3 Vascular Involvement

For the management of acute deep vein thrombosis in BD, glucocorticoids and immunosuppressives such as azathioprine, cyclophosphamide, or cyclosporine A are recommended [68]. Since venous thrombosis in BD is due to inflammation on the vessel wall rather than to a procoagulant state, the use of anticoagulants is still controversial [82]. For the management of pulmonary artery aneurysms, high-dose glucocorticoids and cyclophosphamide are recommended. Anti-TNF agents should be considered in refractory cases. For patients who have or who are at high risk of major bleeding, embolization should be preferred to open surgery [68]. For both aortic and peripheral artery aneurysms, medical treatment with cyclophosphamide and corticosteroids is necessary before surgical intervention, but surgery or stenting should not be delayed if the patient is symptomatic [68].

9.8.4 Neuro-Behçet

High-dose glucocorticoids followed by slow tapering together with immunosuppressives such as azathioprine are recommended for the treatment of acute attacks of parenchymal involvement. Monoclonal anti-TNF antibodies should be started in patients who have severe parenchymal involvement or have persistent or relapsing disease despite corticosteroids and azathioprine and in patients with chronic progressive nervous system involvement [68]. Cyclosporine A can cause an increased risk of nervous system involvement and thus should be avoided in patients with neuro-BD even if CNS involvement is no longer active [68]. Acute venous thrombosis should be treated with high-dose corticosteroids and a short course of anticoagulants (especially in patients with additional thrombotic conditions). The addition of immunosuppressives is still controversial [68].

9.8.5 Other Organ Involvements

Initial treatment for GI involvement is 5-aminosalicylic acid derivatives, while corticosteroids, azathioprine, and anti-TNF agents are needed for more severe and refractory GI disease [29]. Surgical consultation is needed in case of perforation, bleeding, and obstruction [68]. Anti-TNF agents may be added in refractory cases.

Colchicine should be the first-line treatment in BD patients with arthritis. Intra-articular corticosteroids may provide relief in acute attacks, even if this may not be necessary, as the arthritis in BD is usually self-remitting. In recurrent and/or chronic cases, azathioprine, interferon-alpha, or anti-TNF agents can be used [68].

In a systematic review of BD patients, hematopoietic stem cell transplantation, either due to refractory major organ involvement or due to a comorbid hematological condition, was successful in inducing remission in 18 of 19 patients. However, potential adverse events and fatal complications must be kept in mind [83].

9.9 Prognosis

The long-term outcome usually depends on the specific organ involvement. Young age, male sex, and early disease onset are the major poor prognostic factors. Mucocutaneous lesions tend to relapse and remit and do not cause mortality but impair quality of life. Eye involvement, which may lead to total loss of vision, is one of the major causes of morbidity. GI involvement has a remission rate of around 80% and usually can be managed without major treatment options [59]. Neuro-BD is one of the major causes of morbidity and mortality: in a long-term study in adults, 32% of the patients had a progressive course with a 5-year event-free survival rate of 65% [84].

Large vessel involvement, especially bleeding from pulmonary artery aneurysm, is the most common and the main cause of mortality. In a recent series of BD

patients with pulmonary artery aneurysms, 26% of the patients were dead 7 years after onset in spite of treatment with corticosteroids and cyclophosphamide or azathioprine [52]. In a long-term follow-up study of 101 BD patients with vascular lesions, only 38% of them achieved complete remission. The 20-year survival rate was significantly lower in BD patients with arterial involvement (73%) than in those without arterial lesions (89%). Prognosis was even worse in patients with arterial occlusive lesions and in those associated with venous involvement [85].

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Extraintestinal Manifestations of Inflammatory Bowel Disease

10

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Inflammatory bowel diseases (IBD) are chronic inflammatory disorders of the gastrointestinal tract, which include Crohn's disease (CD) and ulcerative colitis (UC). IBD should be regarded as systemic disorders which involve multiple organ systems and could present with various extraintestinal symptoms [1]. Extraintestinal symptoms can be in general divided into two groups: extraintestinal manifestations (EIMs) and extraintestinal complications. Almost every organ system may be affected in IBD including the musculoskeletal system, skin, eyes, hepatobiliary system, lungs, kidneys, immune system, hematologic system, and cardiovascular system [2]. Extraintestinal complications are mainly caused by the disease itself or IBD drug-related side effects [3].

Autoinflammation is becoming increasingly recognized as an important component in the pathogenesis of IBD, especially CD. The new knowledge in the pathogenesis of CD suggests that this multifactorial disease could be classified within the group of autoinflammatory diseases.

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10.1 Epidemiology of Extraintestinal Manifestations

Extraintestinal manifestations may develop in up to 47% of patients with IBD, and some large studies suggest that the prevalence of EIM is higher in CD compared to UC [4, 5]. Extraintestinal manifestations were reported in 25–29% of children and in 6–47% of adult patients with IBD [3, 6].

In the general IBD population, the peak incidence of the disease is in the third decade, but about 25–30% of patients with CD and 20% of patients with UC present before the age of 20 years [3].

In the pediatric population, the peak age of onset is during late adolescence, and 4% of the pediatric IBD is diagnosed before the age of 5 years [7].

Some studies reported more frequent EIM before the diagnosis of IBD in children older than 5 years at the time of diagnosis. In a large cohort of pediatric IBD patients, there were no difference in the risk of development of EIM among different ethnincitis but was found slightly higher risk among girls [8].

10.2 Autoinflammation in the Pathogenesis of Inflammatory Bowel Disease

The etiopathogenesis of IBD is complex and includes interaction between environmental factors and immune system in genetically susceptible individuals. The disease onset is triggered by environmental factors that perturb the mucosal barrier, alter the healthy balance of the gut microbiota, and abnormally stimulate gut immune responses. These three main factors (genetics, gut immune response, and the microbiota) are influenced by the individual's environmental exposures or triggers (the "exposome") to engage different submechanisms [9].

Overall, 163 IBD loci that meet genome-wide significance thresholds were discovered, which is substantially more than in other complex diseases. Most genetic associations are shared between CD and UC (110 loci), and 30 loci were specifically associated with CD. These most strongly and consistently implicate themes involving defective intracellular bacteria killing and innate immunity (CARD15/NOD2, IRGM, IL23R, LRRK2, and ATG16L1) and de-regulated adaptive immune responses, namely, the interleukin-23 (IL-23) and T helper 17 (Th17) cell pathways (IL23R, IL12B (encoding IL-12p40), STAT3, JAK2, and TYK2) [10]. Dendritic cells (DCs) followed by CD4 T cells, natural killer (NK) cells, and NKT cells showed the highest enrichment of these susceptibility gene sets when tested in a panel of immune cell subsets, indicating a major role for these cells in CD pathogenesis [11].

NOD2, autophagy, and Th17 immune responses are three areas most strongly implicated in CD pathogenesis. NOD2 is a cytosolic pattern recognition receptor (PRR) that controls immunity against intracellular bacteria. Three polymorphisms in this gene (amino acid substitutions Arg702Trp and Gly908Arg and the frameshift FS1007insC) are present in 40% of Western patients with CD [12]. NOD2 is expressed in a limited number of tissues that include intestinal epithelial cells (mainly Paneth cells) and monocyte-derived immune cells residing in the lamina propria [13, 14]. In both human and murine studies, defects in NOD2 function can

affect microbial sensing [15], Paneth cell function and antimicrobial peptide production [16], antigen presentation [17], intracellular bacterial killing [18], and innate immune signaling, such as Toll-like receptor (TLR) function [19]. NOD2 activation after recognition of muramyl dipeptide (MDP) triggers nuclear factor kappa-B (NF-kB)-dependent signaling [20] but is relatively weak in this respect compared with other PRRs, such as the TLRs [21]. Deficiency in NOD2 results in enhanced innate TLR signaling. In mice, TLR-mediated IL-12 production is increased in macrophages and DCs deficient in NOD2 [22].

NOD2 gene is causative of Blau syndrome, a granulomatous inflammatory disorder affecting the eyes, skin, and joints [23]. However, in CD NOD2 mutations act as a risk factor, being more common among patients with CD than the background population, while in Blau's disease NOD2 mutations are linked directly to this syndrome. Furthermore, even though inflammation is a common theme in both diseases, CD is associated with chronic granulomatous inflammation of various intestinal segments, often the distal part of ileum including extraintestinal manifestations such as arthritis, uveitis, and skin lesions, whereas Blau's disease is characterized by more diffuse chronic inflammation [24].

Another important pathogenetic mechanism of CD is autophagy. It is a lysosomal degradation pathway that is essential for cell survival, differentiation, development, and homeostasis [25]. Beyond xenophagy, autophagy regulates quality control apparatus, including those involved in control of cell growth, the cell cycle, DNA and membrane repair, and intracellular organelles, such as mitochondria [26]. Defective autophagy can influence cellular homeostasis at the epithelial barrier level in particular and, therefore, represents a crucial component of disease initiation. Polymorphisms in the autophagy genes (ATG16L1, IRGM, and LRRK2) and defective autophagic response to bacteria can contribute to CD [9]. Deficiencies in ATG16L1 protein which is among the highest susceptibility markers could lead to impaired Paneth cell secretions of antibacterial peptides, hyperactivation of the inflammasome, and impaired antigen presentation by antigen-presenting cells [27].

Unresolved endoplasmic reticulum stress in intestinal epithelial cells (IECs) has also emerged as an important factor that initiates gut inflammation relevant to CD [9].

10.3 Musculoskeletal Manifestations

Musculoskeletal manifestations are the most frequent EIM in CD and UC [2, 4, 28–30]. Articular involvement occurs in almost 40% of patients suffering from IBD [2, 30]. Arthropathies in IBD are often associated with increased morbidity resulting in a worse quality of life in comparison to IBD patients without arthropathies [2, 4, 28–33].

10.3.1 Pathogenesis

The mechanism of the development of arthritis in IBD remains to be defined. There are several theories that try to explain the pathogenesis of arthropathy in the setting of IBD [34, 35]. The first theory includes translocation of bacteria across the

disturbed intestinal barrier and adaptive immune response. Translocated bacteria trigger an adaptive response which due to shared epitopes is incapable to distinguish between epitopes of bacteria and epitopes of synovia leading to an autoimmune process [34–39]. The second theory involves intestinal lymphocytes and their migration to various tissues which depends on various receptors and adhesion molecules. Binding of intestinal lymphocytes to synovial tissue vessels is based on vascular adhesion protein-1 (VAP-1) that supports the binding of all leukocytes. This means that gut lymphocytes might migrate to the synovium and cause inflammatory arthritis. According to one study, not only intestinal lymphocytes but also macrophages expressing the scavenger receptor CD163 were found in the gut and in synovia in IBD patients. Another study reported that mesenchymal cells of intestines and joints may be targets for TNF-mediated inflammation [40–45]. The HLA-B27/human β2-microglobulin transgenic rat model demonstrated that intestinal bacteria are necessary for the development of B27-associated gut and joint inflammation. This animal model showed that rats developed chronic inflammation of both the stomach and colon. The rats also developed an axial and peripheral arthritis, which was similar to human spondyloarthropathy. Intestinal and synovial inflammation did not appear in B27 transgenic rats kept in environment without bacterial exposure. The gut and joint inflammation reappeared after exposure to normal intestinal bacteria. This rat model suggests that intestinal bacteria play a role in the development of spondyloarthropathies in proper genetic background [39, 46].

10.3.2 Clinical Manifestations

10.3.2.1 Peripheral Arthritis

Peripheral arthritis in patients with IBD manifests typically as a seronegative arthritis. It is known that peripheral arthritis occurs more frequently in patiens with CD than in those with UC. IBD patients with colon involvement have a higher risk for peripheral arthritis [47]. Peripheral arthritis is divided into two main groups: type I or pauciarticular arthritis and type II or polyarticular arthritis [48, 49]. Type I arthritis affects fewer than five joints and usually affects large joints such as the hips, knees, ankles, shoulders, elbows, and wrists. Symptoms of joint inflammation in type I arthritis are usually acute, asymmetrical, and self-limiting and resolve in maximum duration of 10 weeks. Frequently pauciarticular arthritis does not damage joints permanently and mostly appears during exacerbations of IBD activity [3, 50–52].

Type II arthritis affects more than five joints and usually involves small joints of upper limbs in a symmetrical distribution. Type II arthritis does not correlate with IBD activity and may precede the intestinal symptoms. It may last for months to years [3, 50–52].

The diagnosis of type I and type II arthropathies in IBD is based on clinical manifestations. The two types of arthropathies are seronegative but might be related to immunogenetical entities. Type I arthropathy is more associated with HLA-B27, HLA-B35, and HLA-DR103. Type II arthropathy is associated with HLA-B44.

Imaging studies are usually with no significant evidence of inflammation or joint destruction [3, 48–52].

10.3.2.2 Axial Arthropathies

Axial arthropathies include ankylosing spondylitis and sacroiliitis. If compared to peripheral arthropathies, axial arthropathies are less frequent and appear in up to 5% of IBD patients. The course of axial arthropathies does not correlate with that of IBD [3, 53].

Ankylosing spondylitis (AS) is a chronic inflammation of the axial skeleton. AS appears in up to 10% of patients suffering from IBD. Usually AS in IBD patients is HLA-B27 positive. AS starts at young age and manifests as severe lower back pain and morning stiffness. AS diagnosis is supported by radiographs which show vertebral sclerosis [3, 53]. Sacroiliitis (SI) is an inflammation of the sacroiliac joints. SI might occur in up to 32% of patients with IBD and could be unilateral or bilateral. SI is usually asymptomatic and HLA-B27 negative. IBD patients with SI usually present with pelvic pain and might have decreased spinal mobility. Sacroiliitis is diagnosed by magnetic resonance imaging or at a later stage by radiographs which show sclerosis and erosions of sacroiliac joints [3, 53].

10.3.3 Treatment

Type I peripheral arthropathy is associated with the activity of IBD course. Therefore, the treatment of type I arthropathy is based on the anti-inflammatory treatment of IBD. The course of type II peripheral arthropathy is independent from the activity of IBD. Consequently, the treatment of type II arthropathy is based on nonsteroidal anti-inflammatory drugs, selective cyclooxygenase (COX)-2 inhibitors, or analgesics. Other treatment options include local steroid injection into the joints and physiotherapy. The treatment of axial arthropathies includes 5-ASA medications, methotrexate (MTX), azathioprine, and antitumor necrosis factor-α (anti-TNFα) therapy. Anti-TNF-α antibodies might be used in refractory cases [54–60].

10.4 Skin Involvement

Cutaneous manifestations are also one of the most common EIMs with reported prevalence between 22% and 75% for CD and between 5% and 11% for UC [61].

The most frequent skin manifestations are erythema nodosum (EN), pyoderma gangrenosum (PG), and aphthous stomatitis (oral ulceration).

During the course of the disease, a great variety of skin lesions may develop, many of which are secondary to granulomatous cutaneous disease, reactive skin eruptions, nutritional deficiency, and other associated conditions [62, 63].

Some extraintestinal skin manisfestations correlate with the disease activity of IBD (e.g., erythema nodosum, Sweet's syndrome), while others (e.g., pyoderma gangrenosum) are independent of intestinal manifestations.

10.4.1 Pathogenesis

Mucosal T cells are important in maintaining intestinal homeostasis defined as the balance between the mucosal epithelium, intestinal microbes, and host immune response. Abnormal T-cell response to the microbial antigens can disrupt this equilibrium and is believed to be the mechanism that triggers the chronic inflammation and excessive secretion of cytokines that lead to the development of IBD [7].

10.4.2 Clinical Manifestations

According to the pathogenesis, cutaneous manifestations of IBD can be classified into the following four categories:

- Specific cutaneous manifestations or granulomatous cutaneous lesions with the same histological features as the underlying bowel disease
- Reactive cutaneous manifestations of IBD with immunological mechanisms triggered by common antigens shared by the gut bacteria and skin
- Cutaneous disorders or dermatosis associated with IBD
- Secondary cutaneous manifestations either due to the complications of IBD or adverse effects of IBD treatments

10.4.2.1 Cutaneous Manifestations with the Same Histological Features as the Underlying Bowel Disease

Cutaneous Crohn's Disease

Cutaneous or metastatic CD is a rare complication of IBD. Cutaneous lesions are characterized by the presence of specific noncaseating granulomas with multinucleated giant cells in the dermis surrounded by lymphocytes, plasma cells, and eosinophils similar as the intestinal lesions [64]. It occurs more frequently in adult females with established intestinal CD [64].

Clinically, skin lesions present as subcutaneous nodules (Fig. 10.1) or nonhealing ulcers in the lower extremities with rare localization to the genital (vulvar or testicular) area [64, 65].

Cutaneous CD can be divided into two clinical forms [66]: the genital form (56%) which occurs more frequently in children (characterized by edema, erythema, fissures or ulcers of the labia, scrotum, or penis) and the non-genital form (44%), which most commonly affects the lower extremities (38%), abdomen and trunk (24%), upper extremities (15%), face and lips (11%), and intertriginous areas (8%).

These cutaneous lesions are not associated with activity of the bowel disease or its response to the IBD treatment [67].

Various treatment modalities have been tried, such as steroids (topical, intralesional, or systemic), sulfasalazine, metronidazole, azathioprine, MTX, hyperbaric oxygen, and anti-TNF-α antibodies [67]. In cases with severe cutaneous ulcers

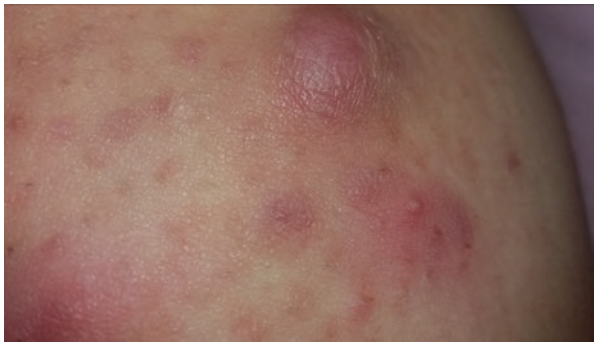

Fig. 10.1 Subcutaneous nodules and maculopapules

unresponsive to medical treatment, surgical resection under oral administration of zinc sulfate may be indicated [64].

Perianal Manifestations

Perianal CD includes erythema, abscesses, ulcers, fissures. and fistulas, which occur in approximately 50% of CD patiens [5, 68].

Perianal fissures and fistulas are one of the most common skin lesions of IBD and occur mainly in CD (20–60%) and rarely in UC [68]. Perianal fissures and fistula are due to direct involvement of skin and mucosa via similar mechanisms as the bowel disease and may antedate the signs and symptoms of IBD by several years [68]. Fissures are usually painless and located posteriorly, whereas fistulas manifest either as a cryptoglandular infection or as a secondary complication of anal fissures [5].

The most suitable treatment of perianal fissures and fistulas are combined medical and surgical therapies. Medical treatment include topical applications of glyceryl trinitrate (nitroglycerine) ointment, antibiotics (metronidazole, ciprofloxacinum), immunosuppressants (azathioprine, 6-MP, cyclosporine, tacrolimus), and anti-TNFα drugs [68].

Orofacial Manifestations

Orofacial involvement occurs in 5–20% of CD patients and can present as aphthous stomatitis, pyostomatitis vegetans, angular cheilitis and ulceration, mucosal nodularity (cobblestoning of the buccal mucosa), nodules of gingival and alveolar mucosa, and indurated fissuring of lower lips [64, 68].

10.4.2.2 Reactive Cutaneous Manifestations of Inflammatory Bowel Disease

Erythema Nodosum

Erythema nodosum is the most common skin lesion and correlates with symptoms of active bowel disease [19]. Erythema nodosum occurs in up to 15% of patients with CD and 10% of patients with UC [4, 69]. It is most common in females and

frequently associated with large-intestine involvement and eye and peripheral arthritis involvement [3].

This manifestation tends to present during the first 2 years of the clinical course of the disease and may reocurr in approximately one-half of cases [62].

Histological examination of the lower dermis in these patients may reveal a moderate lymphohistiocytic infiltrate, and direct immunofluorescence for immunoglobulins and complement may reveal perivascular deposits [70].

Erythema nodosum is usually easily recognized as raised, tender, red, or violet inflammatory subcutaneous nodules of 1–5 cm in diameter, typically on the anterior extensor surface of the lower extremities but rarely on the face and trunk [4]. The nodules tend to persist for several weeks to months. As they heal, they frequently leave pigmented areas (Fig. 10.2) that persist for many months. Microscopic examination shows lesions characterized by lymphohistiocytic infiltrate of the lower derma, defined as septal panniculitis.

The diagnosis is established based on clinical judgment, and skin biopsies are rarely required [3].

Erythema nodosum usually heals without scars. Its onset coincides with acute flares of IBD and is frequently self-limiting or improves with treatment of the underlying IBD [3, 33].

Mild cases may be treated with leg elevation, use of analgesics, potassium iodine and compression stockings [1].

Erythema nodosum lesions respond well to treatment with corticosteroids, but severe or refractory cases may require anti-TNFα therapy [71].

In severe or refractory cases, alternative causes of erythema nodosum should be investigated such as infections with *Streptococcus*, *Yersinia pseudotuberculosis*, *Yersinia enterocolitica*, syphilis, sarcoidosis, Behcet's disease, and use of oral contraceptives or other medication. After exclusion of other causes, severe cases may require systemic corticosteroids, immunosuppressive therapy, or anti-TNFα

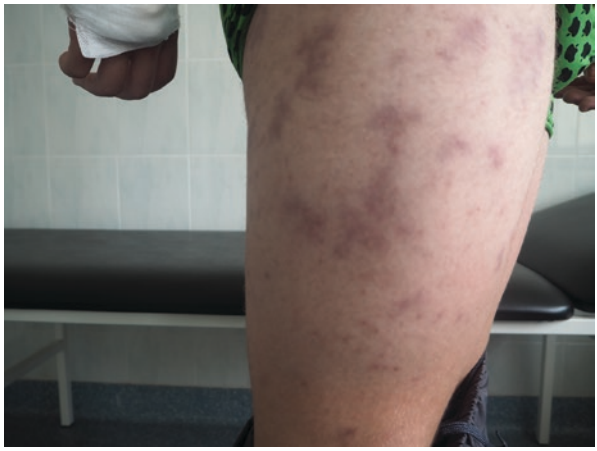

Fig. 10.2 Erythema nodosum resolves to pigmented areas

antibodies. Only a few case reports highlight the benefit of infliximab and adalimumab for erythema nodosum [70, 72].

Pyoderma Gangrenosum

Pyoderma gangrenosum is a much rarer, but more severe and more common in UC than in CD [3]. It is the second most common dermatologic manifestation of IBD.

It affects women more frequently than men [73] and is associated with black African origin, familial history of UC, and pancolitis as the initial location of IBD, permanent stoma, eye involvement, and erythema nodosum [69].

The prevalence of pyoderma gangrenosum in IBD is 0.4–2% [1, 2, 28, 74].

On the contrary, up to 50% of patients with pyoderma gangrenosum have underlying IBD [4]. The lesions are usually preceded by a trauma (even many years earlier) through a phenomenon known as pathergy. This trauma can even be minimal such as venous puncture or biopsy [75].

Patients with severe disease and colonic involvement are most likely to develop this complication. The disease course is unpredictable. Pyoderma gangrenosum usually begins as an erythematous pustule or nodule that spreads rapidly to the adjacent skin and develops into a burrowing ulcer with irregular violaceous edges [76].

The deep ulcerations often contain purulent material, which is sterile on culture (Fig. 10.3). These ulcers can be solitary or multiple, unilateral, or bilateral and can range in size from several centimeters to an entire limb. The most common sites includes extensor surfaces of the legs (shins) and adjacent to a postsurgical stoma but can occur anywhere on the body including the genitalia [76].

There are no pathognomonic histological features, generally revealing only diffuse neutrophil infiltration and dermolysis. Pyoderma gangrenosum has typically no association to the clinical activity of the underlying intestinal disease; however, pyoderma gangrenosum may resolve with treatment of the IBD [28].

Peristomal pyoderma gangrenosum is seen occasionally as a complication in patients with IBD.

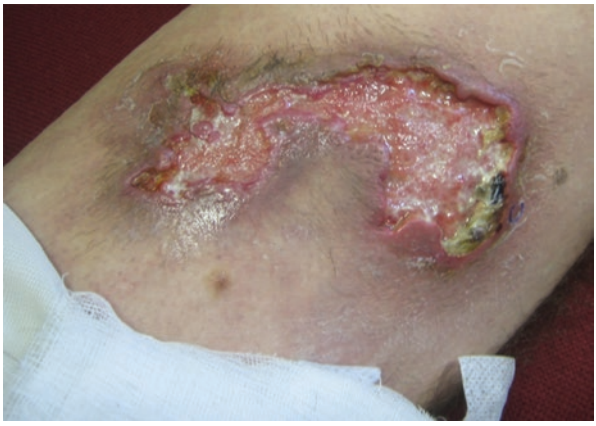

Fig. 10.3 Pyoderma gangrenosum

Mild cases usually respond to local and topical therapy, including intralesional corticosteroid injections, moist treatment with hydroactive dressings, and topical sodium cromoglycate [3, 76, 77].

Effective systemic agents include oral sulfasalazine, dapsone, corticosteroids, and immunomodulators such as azathioprine, cyclophosphamide, cyclosporine, methotrexate, tacrolimus, and mycophenolate mofetil [1, 3, 76, 77].

Intravenous cyclosporine and anti-TNFα drugs were tried in some of those patients with good clinical success.

Pyoderma gangrenosum is initially sometimes treated by surgical debridement. A surgical intervention typically worsens PG. If there is any doubt about the nature of an ulcer in patients with IBD, surgical debridement should be avoided until a PG is excluded. It has been discussed whether a maintenance treatment also is necessary for PG.

Sweet's Syndrome

Sweet's syndrome was first described by R. D. Sweet in 1964, when he reported a case of "an acute febrile neutrophilic dermatosis" [78]. It's a rare dermatologic manifestation characterized by the abrupt onset of tender and red to purple inflammatory nodules or papules that join to form plaques, affecting the upper limbs, face, or neck (Fig. 10.4) [68]. In addition to painful and edematous nodules and plaques, vesicles, bullae, or pustules may also be present [64].

This manifestation is rare in children. Sweet's syndrome may be associated with systemic manifestations—arthritis, fever, and ocular symptoms, such as conjunctivitis or episcleritis. Patients may also experience fatigue, headache, and other nonspecific constitutional symptoms.

Skin lesions are tender and nonpruritic in nature but can be difficult to distinguish from erythema nodosum when they affect the lower extremities [79]. Skin biopsy can help to establish the correct diagnosis; it shows neutrophilic infiltrates in the reticular dermis without evidence of vasculitis [1, 79, 80].

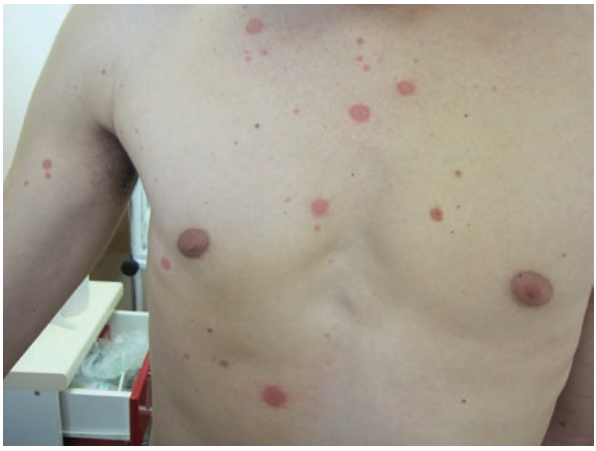

Fig. 10.4 Red inflammatory nodules and papules

Table 10.1 Diagnostic criteria for Sweet's syndrome[a] [85]

1. Abrupt onset of painful erythematous plaques or nodules
2. Histopathologic evidence of a dence neutrophylic infiltrate without evidence of leukocytoclastic vasculitis
3. Pyrexia >38
4. Association with an underlying hematologic or visceral maligancy, inflammatory disease, and pregnancy or preceded by an upper respiratory or gastrointestinal infection or vaccination
5. Excellent response to treatment with systemic corticosteroids or potassium iodide
6. Abnormal laboratory values at presentation (three out of four): erythocyte sedimentation rate > 20 mm/h, positive C-reactive protein, and >8000 leukocytes and >70%neutrophilis

[a]The presence of both major criteria (1 and 2) and two minor criteria (3, 4, 5, and 6) is required to establish the diagnsosis of classical Sweet's syndrome.

Although the pathogenesis is unclear, Sweet's syndrome usually develops as a reactive response and may be associated with other systemic diseases, such as infection, malignancy, medications, or IBD [81].

Pathogenesis of Sweet's syndrome has been hypothesized to be related to an altered immune response to common antigens in the skin and gut bacteria [82]. Furthermore, ANCA and G-CSF or other cytokines have been proposed to play a pathogenetic role in activation, maturation, and chemotaxis of neutrophils in Sweet's syndrome [47].

At first diagnostic criteria for Sweet's syndrome were proposed by Su and Liu in 1986 [83, 84]. In 1994 they were modified by von den Driesch (Table 10.1) [85].

When dealing with localized disease, topical or intralesional steroids are sometimes used with good effects [1]. Skin lesions that have not been treated have been documented to heal on their own but can leave behind scars [1]. Most cases of Sweet's syndrome respond to topical or systemic corticosteroid therapy and heal without scarring.

Other first-line options for treatment include colchicine and potassium iodide. Other agents such as indomethacin and clofazimine can be used if first-line agents are ineffective or cannot be tolerated [78, 86]. Treatments with immunosuppressants and anti-TNF-α have been reported to be successful in Sweet's syndrome [86, 87].

Bowel-Associated Dermatosis-Arthritis Syndrome (BADAS)

The origin of BADAS is postulated as bowel bypass syndrome as it was originally reported to occur in up to 20% of patients after laparoscopic jejunoileal bypass surgery for obesity. It can also occur as a complication after various intestinal surgeries, in patients with diverticulitis or appendicitis and in patients with IBD [64, 88, 89].

BADAS is neutrophilic dermatosis characterized by fever and/or flu-like symptoms, followed by myalgias, malaise, abdominal pain, arthritis, and polyarthralgias of the upper extremities involving the asymmetric large joints and interphalangeal joints of the fingers with accompanying tenosynovitis, and by the appearance of characteristic cutaneous lesions [88].

These cutaneous lesions consist of erythematous macules (3–10 mm in diameter) developing into edematous and painful papules with central aseptic vesicles or

pustules (2–4 mm in diameter) (Fig. 10.5), which are mostly located on the upper chest and arms (usually on the deltoid muscle region) and erythema nodosum-like lesions in the legs. These maculopapular rashes occur in crops, resolve within 1–2 weeks without leaving scars, and can recurr every 1–6 weeks [88, 89].

It has been hypothesized that BADAS occurs as an immune reaction to bacterial overgrowth in the bowel of patients with IBD, infection, or surgery. The reaction is in response to a bacterial antigen and manifests cutaneously [90]. The circulating immune complexes usually form due to an immunological response against antigenic bacterial peptidoglycans in the gut, with subsequent deposition in the skin and joints [89]. This same pathogenesis is thought to cause various other manifestations

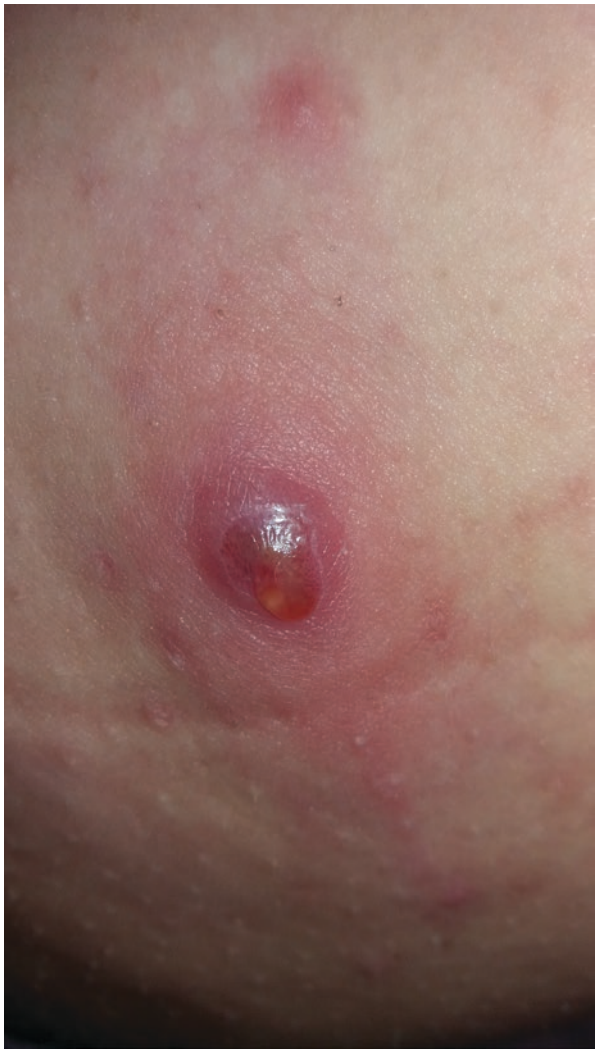

Fig. 10.5 Edematous tensed vesicle with surrounding erythema

of CD such as erythema nodosum. Bacteria that incite this immune response include *Bacteroides fragilis*, *Escherichia coli*, and *Streptococcus*.

Similar to pyoderma gangrenosum and Sweet's syndrome, BADAS has been classified in the spectrum of aseptic neutrophilic dermatoses with histopathology showing dense neutrophil infiltration and no destruction of vessel walls [89, 90].

The histology of BADAS shows perivascular neutrophilic, mononuclear, and eosinophilic (depending on the stage of the lesions) infiltrate with dermal edema, intraepidermal pustules, and minimal alterations of the walls of capillaries and venules without the features of leukocytoclastic vasculitis or fibrinoid necrosis [64, 91].

The management of the BADAS includes treatment of the underlying bowel disorder as well as the administration of systemic steroids and antibiotics for inhibition of bacteria overgrowth (tetracycline, metronidazole, ciprofloxacin) [80]. However, response to antibiotics often is variable [88, 91].

NSAIDs may be used to reduce arthralgias or arthritis, but the potential toxicity of NSAIDs on IBD should make the decision to use NSAIDs based on weighing the risk-benefit ratio for each individual patient [54]. Other drugs such as colchicine, dapsone, and sulfasalazine have been tried with variable successful rates [64].

Leukocytoclastic Vasculitis

Leukocytoclastic vasculitis is an uncommon EIM in patients with IBD.

This is an immune complex syndrome involving small vessels characterized by neutrophilic invasion, endothelial damage, and fibrinoid necrosis. Lesions are classically appearing as palpable purpura but may also develop as necrotic ulcers (Fig. 10.6).

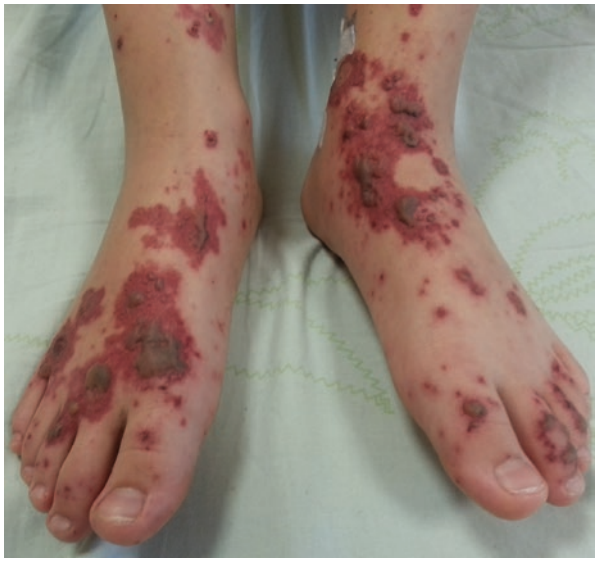

Fig. 10.6 Leukocytoclastic vasculitis with necrotic ulcers

Similar to other reactive cutaneous manifestations of IBD, the pathogenesis of leukocytoclastic vasculitis is associated with hypersensitivity vasculitis of small vessels [92, 93].

In CD, leukocytoclastic vasculitis occurs not only during the onset of bowel disease but also during periods of exacerbation. On the other hand, in UC, leukocytoclastic vasculitis most commonly precedes the onset of bowel disease with a laging period from 1 month to 2 years [93, 94]. In most cases of leukocytoclastic vasculitis, treating the underlying IBD results in resolution of the lesions [94, 95].

10.4.2.3 Cutaneous Disorders or Dermatoses Associated with Inflammatory Bowel Disease

These disorders include hidradenitis suppurativa, phlebitis, erythema multiforme, urticaria, lichen planus, secondary amyloidosis, and various autoimmune skin disorders, such as acquired epidermolysis bullosa (blistering lesions of the knees, elbows, hands, and feet), bullous pemphigoid, linear IgA bullous dermatosis, vitiligo, and psoriasis [64, 68].

The most frequently associated cutaneous disease is psoriasis which occurs in 7–11% of the IBD population compared to 1–2% in the general population [5]. In one study, psoriasis was found to be more prevalent in CD (11.2%) than in UC (5.7%) [1, 96]. The association of IBD with psoriasis is believed to be both genetically and immunologically related [64]. Psoriatic skin lesions are pruritic and irritated scaly patches (Fig. 10.7), which can be associated with nail changes and arthritis. They most frequently occur on the elbows, kness, trunk but can occur anywhere.

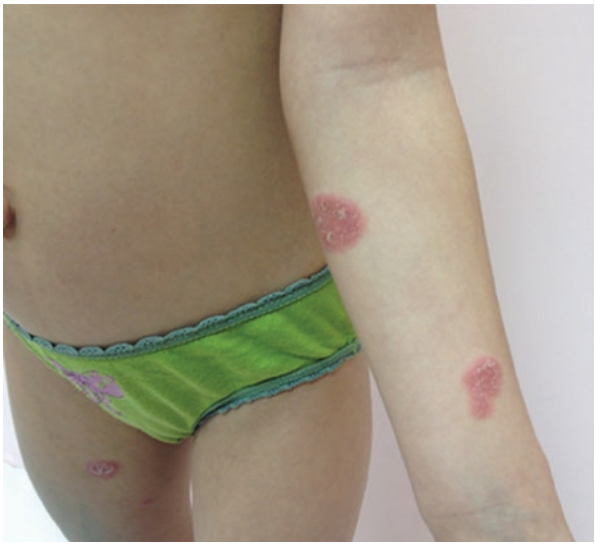

Fig. 10.7 Irritated scaly patches

10.5 Oral Lesions

The prevalence rate of oral manifestations in IBD is estimated to be between 20% and 50% in most publications [97, 98]. In pediatric patients, the highest reported prevalence was 48% [98].

10.5.1 Indurated Tag-Like Lesions

Indurated tag-like lesions are specific for CD and are described as white reticular tags [99], mostly seen in the labial and buccal vestibules and in the retromolar regions [100]. In most cases, up to 75% noncaseating granulomas can be observed on histopathology [98].

10.5.2 Cobblestoning

Cobblestoning is another specific oral lesion for CD. Cobblestoning is described as fissured swollen buccal mucosa with corrugation and hyperplastic appearance of the mucosa [97, 101]. Usually, it is seen in the posterior buccal mucosa and may consist of mucosal-colored papules that produce firm plaques. Patient can present with pain of mucosa and could cause eating difficulties [102]. These lesions can be treated with topical steroids in addition to the main treatment of IBD. In severe cases, systemic steroids could be used [103].

10.5.3 Aphthous Stomatitis

Aphthae are shallow round ulcerations with central fibrinous exudate and erythematous border (Fig. 10.8) [77]. Aphthous stomatitis has been associated with other diseases such as ankylosing spondylitis, uveitis, peripheral arthritis, and erythema nodosum [31].

In the general population, these lesions may occur in 20–25% [50], in up to 10% of patients with UC, and in 20–30% of those with CD that have oral aphthosis [104]. The presence of aphthous stomatitis does not correlate with intestinal disease activity but may become more severe in active disease. Factors including geographic variation, gender, smoking, breastfeeding, and hormonal stress have been postulated to affect the disease [105].

Recurrent ulceration can clinically lead to significant odynophagia and dysphagia [100].

Aphthous eruptions are not specific to IBD and may be found in other diseases, such as Behçet's disease, Reiter's syndrome, HIV/AIDS, and celiac sprue, as well as in apparently healthy population [77].

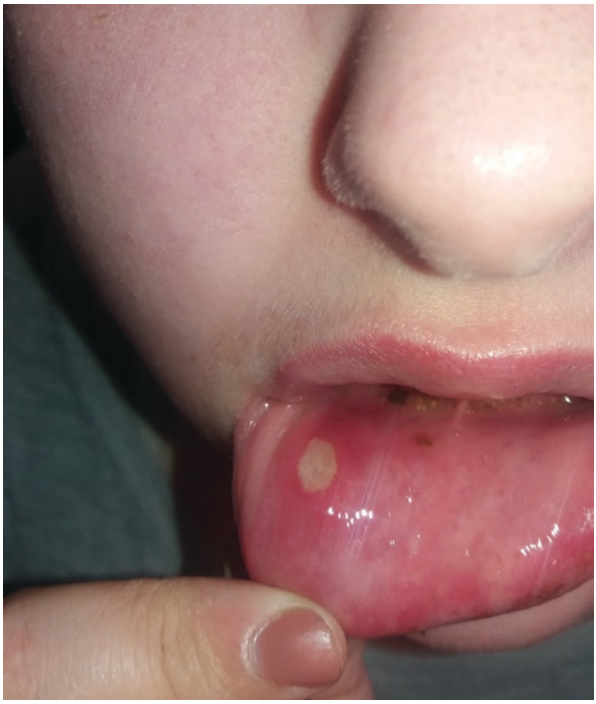

Fig. 10.8 Aphtous stomatitis and ulceration with central fibrinous exudate

Management of CD is usually sufficient for control of oral aphthosis. For control of pain, topical agents (such as lidocaine) and/or topical steroids (such as triamcinolone 0.1%) up to three times per day can be used. Dexamethasone elixir (0.5 mg/5 mL spit or swish) or ointment up to three times per day is also efficacious. Nonsteroidal anti-inflammatory pastes are effective in relieving pain and promoting healing. Systemic or intralesional steroids should be reserved for severe refractory and/or persistent cases [104, 106, 107].

10.5.4 Pyostomatitis Vegetans

Pyostomatitis vegetans was first described in 1949 [108]. These lesions are relatively rarely found, but are associated with IBD, and occurr more frequently in patients with UC than patients with CD [109].

There is a predilection for males with a male/female ratio of nearly 3:1. These lesions can occur at any age but are more prevalent in patients between 20 and 59 years of age with an average age of 34 years [110, 111].

Despite every effort, no bacterial, fungal, or viral causes have yet been found for this manifestation, and its pathogenesis remains obscure [112].

Histological features are intraepithelial and subepithelial microabscesses with large numbers of eosinophils and neutrophils. Hyperkeratosis and acanthosis can

also be present [109]. Direct immunofluorescence in pyostomatitis vegetans is negative for deposits of IgA, IgG, and C3, and this result is helpful in distinguishing pyostomatitis vegetans from pemphigus vulgaris [97, 113].

Patients may experience severe oral discomfort, which is not related to clinical activity of UC [114, 115]. Pain intensity is variable; some patients with extensive oral lesions may not have any pain. Other symptoms include fever, enlarged and tender submandibular lymph nodes, and pain [115]. Pyostomatitis vegetans can involve almost any part of the oral cavity but is most frequently observed on the labial attached gingiva (Fig. 10.9), soft and hard palate, buccal mucosa, and vestibular gingivae. The least common locations are the floor of the mouth and the tongue [110].

The diagnosis of pyostomatitis vegetans is based on a constellation of clinical features that include concurrent IBD, peripheral eosinophilia, histological study, and negative culture results of the lesion exudate. A negative immunofluorescence study is also helpful [97, 115]. Biopsies may show microabscesses below the epidermis with neutrophil and eosinophilic infiltrate [116]. Herpetic infections should be excluded by Tzanck smear, antigen detection, and the culture of the virus or PCR for HSV virus [77].

The main differential diagnoses of pyostomatitis vegetans include vesicular disorders involving both the skin and oral cavity, similar to pemphigus vulgaris in particular, as well as other diseases like bullous pemphigoid, acquired epidermolysis bullosa, bullous drug eruptions, herpetic infection, Behçet's disease, and erythema multiforme [97, 112].

The mainstay in the management of pyostomatitis vegetans is the treatment of underlying IBD. Topical steroids and antiseptic mouthwashes alone are effective in only a few instances. Systemic steroids are usually prescribed for these patients and are considered as the treatment of choice. Azathioprine and sulfamethoxypyridazine can be used in parallel with steroids as sparing agents [112, 115, 117].

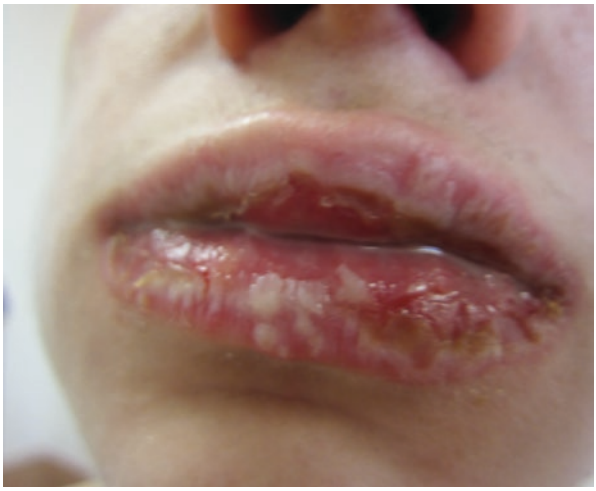

Fig. 10.9 Pyostomatitis vegetans

10.6 Ophthalmologic Manifestations

Ocular manifestations are among the most common EIMs. In adult population, uveitis and episcleritis were described as one of the most commonly reported conditions with a prevalence between 2% and 6% [118, 119], and even higher prevalence was reported when taking into account other ocular conditions [119, 120].

Overall prevalence of ocular EIMs in IBD at diagnosis ranged from 0.62% to 1.81%. Prevalence during follow-up ranged from 0.69% to 1.82% [121]. Children with CD were found to be at increased risk for developing ocular EIMs [121].

Pathophysiology of ocular EIMs remains unclear. Several studies suggested that local action of antigen-antibody complexes produced against the bowel wall vessels and transported via the bloodstream could be responsible for eye involvement [122, 123]. Also it has been suggested that there is a link between systemic disease and uveitis due to disturbance in physiological macrophage-mediated autophagy [124].

10.6.1 Episcleritis

Episcleritis is a benign inflammation of the episclera, which is a thin blood-rich layer of tissue that covers the sclera. It is the most common ophthalmological manifestation [125]. Clinically, episcleritis causes moderate discomfort and acute redness in one or both eyes [125]. Diffuse or localized episcleral edema can also be present [126]. Episcleritis commonly appears during the flares of IBD.

Slit-lamp examination is essential for diagnosis of episcleritis. Episcleral injection blanches with topical application of phenylephrine and softens with palpation [127].

Differential diagnosis should be made between uveitis and scleritis and is based on the absence of moderate to severe eye pain, photophobia, blurring, and low vision in the former [128]. Differentiation with conjunctivitis may be difficult [5].

Usually it is a benign condition and treatment is not always necessary. In some cases cool compresses, lubricant eye drops, topical nonsteroidal anti-inflammatory drugs, and topical corticosteroids can be prescribed [128, 129].

10.6.2 Scleritis

Scleritis is an inflammation of the sclera, the opaque, and the protective outer layer of the eye [125]. If left untreated scleritis, it can progress to permanent visual loss [128]. Scleritis is classified according to the location (anterior and posterior) and clinical presentation (diffuse, nodular, or necrotizing) [130]. The necrotizing anterior scleritis is classified according to etiology (vaso-occlusive, granulomatous, surgically induced, scleromalacia perforans).

Scleritis is much rarer than episcleritis and occurs in less than 1% of cases [128].

Clinically, scleritis manifests with ocular pain which radiates to the face and scalp. Usually it worsens at night and is associated with ocular hyperemia and visual loss [125]. Involvement of the anterior part of the sclera is more common; posterior scleritis is not associated with ocular hyperemia.

Scleritis should be investigated with caution, and systemic treatment is essential in all cases. Patient can be treated with oral nonsteroidal anti-inflammatory drugs. In severe cases, systemic steroids or immunosuppressive drugs may be prescribed. One of the most important aspects is control of the underlying bowel disease to prevent further recurrence [131].

Recurrent scleritis can lead to scleromalacia, retinal detachment, or optic nerve swelling [132].

10.6.3 Uveitis

Uveitis is defined as inflammation of the uveal tract, the middle layer of the eye, which includes the iris, ciliary body, and choroid. Uveitis is classified into anterior, intermediate, and posterior based on the affected coat. Anterior uveitis affects the iris and ciliary body. Intermediate uveitis affects the vitreous body, and posterior uveitis affects the chorioid or retina. The term panuveitis is used if inflammation involves all layers of the uvea of the eye. Uveitis can occur during active bowel disease and during relapses or may precede by years the diagnosis of IBD [133].

Anterior uveitis presents with acute onset of a red, painful eye, and variably blurriness in vision, and the main symptom is photophobia [133].

Slit-lamp examination confirms the diagnosis with findings of anterior chamber cells and keratic precipitates, which are inflammatory deposits on the endothelial surface of the cornea.

Initial treatment of uveitis includes the use of topical corticosteroids [133] to reduce inflammation and topical cycloplegics to prevent ciliary body and pupillary spasms related to ocular pain. Cycloplegics also prevent posterior synechiae [128]. In case of posterior uveitis, deeper penetration might be required. Systemic treatment is used only for refractory cases. In case of bilateral uveitis, oral steroids are indicated; other drugs such as methotrexate, mycophenolate mofetil, and cyclosporine might be used [134]. In case of refractory, sight-threatening uveitis, anti-TNFα agents such as adalimumab or infliximab should be considered [134].

Long-term complications of uveitis are intraocular adhesions due to chronic inflammation, which can lead to secondary glaucoma or cataract [133].

Ocular complications occur more frequently in patients with CD [120] than in patients with UC, and an association has been reported with female sex [135]. Exceptionally rare ocular manifestations of IBD include central artery occlusions, retinitis, optic neuritis, orbital inflammatory disease, keratitis and central retinal vein occlusion. Orbital myositis, with intermittent proptosis and periorbital swelling, has rarely been reported as the presenting symptom of CD [136].

Table 10.2 Hepatobiliary issues to consider in patients with inflammatory bowel disease [121]

1. Extraintestinal manifestations	*Immune-related*: • Primary sclerosing cholangitis • Autoimmune hepatitis • Autoimmune sclerosing cholangitis *Thrombotic disorders*: • Portal vein thrombosis • Venous thromboembolism • Hepatic vein thrombosis
2. Medication toxicity	• Glucocorticoids • Sulfasalazine • Thiopurines • Methotrexate • Anti-TNFs
3. Underlying hepatic disorder unrelated to IBD	• Cholelithiasis • Viral hepatitis • Transplant issues • IgG4 cholangiopathy • Granulomatous hepatitis • Primary biliary cirrhosis • Hepatic amyloidosis • Nonalcoholic fatty liver disease/steatohepatitis

10.7 Hepatobiliary Manifestations of Inflammatory Bowel Disease

Hepatobiliary manifestations of IBD are common in children. Elevated liver enzymes episode was found in 43–58% of patients [137, 138]. The cause of these elevations falls into the three categories (Table 10.2) [139]:

- Extraintestinal manifestations of the IBD
- Related to medication toxicity
- The result of an underlying primary hepatic disorder unrelated to IBD

Most of the patients had hepatic (69%) and less frequently cholestatic (8%) or mixed character of elevated liver enzymes. Usually elevated liver enzymes episode is idiopathic (87%) and benign, transient finding with no significant differences in character, chronicity, or degree between CD and UC [137]. Among most common etiological factors of elevated liver enzymes are corticosteroids, antibiotics, and exclusive enteral nutrition which demonstrated strongly positive associations with the first development of abnormal elevated liver enzymes [138].

10.7.1 Immune-Related Manifestations

10.7.1.1 Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic, progressive, cholestatic liver disease with inflammation and fibrosis of the intrahepatic and extrahepatic bile ducts,

with multifocal bile duct strictures [139]. Approximately 75% of children with primary sclerosing cholangitis also have IBD [140]. PSC is more prevalent in UC up to 50% and less frequent in CD (11%) [141]. There is a male predominance when PSC is associated with UC [142]. Among IBD patients, PSC occurs in 4% or less [143]. PSC may precede the onset of, coincide with, or follow the diagnosis of IBD. Intestinal inflammation in a patient with PSC may represent a unique phenotype of IBD, termed PSC-IBD, which is genetically and clinically distinct from IBD alone [141]. It is characterized by pancolitis, rectal sparing, and possibly backwash ileitis, as well as a threefold increased risk of colorectal dysplasia [144], but IBD is less severe than in UC alone [145]. Patients with colitis and PSC have increased risk of active and histologic disease in the absence of symptoms compared to individuals without PSC [140].

Clinical Presentation

PSC symptoms are secondary to cholestasis and progressive liver fibrosis, including jaundice, hepatomegaly, splenomegaly, recurrent cholangitis, and intractable pruritus [146].

The diagnosis of PSC is based on a cholestatic serum biochemical profile (gamma-glutamyl transpeptidase (GGT) of >252 U/L had sensitivity (99%) and specificity (71%) [138]) with characteristic changes on liver histology (fibro-obliterative cholangitis, periductal fibrosis) and/or cholangiography (multifocal bile duct strictures and segmental dilations) typically initially imaged by magnetic resonance cholangiopancreatography (MRCP) and confirmed by endoscopic retrograde cholangiopancreatography (ERCP) if needed [147].

Treatment

There is no drug which could alter the natural history of PSC. Liver transplantation remains the only option for progressive PSC.

Ursodeoxycholic acid has been extensively studied in adult PSC, and doses of 17–23 mg/kg/day will generally lead to improvement in liver biochemistries, but patient survival has not improved. The higher doses should be avoided in children due to adverse effects.

Antibiotic therapy is considered as experimental. Oral vancomycin completed normalization in ALT, GGT, and erythrocyte sedimentation rate in all noncirrhotic pediatric patients [138] and only in 0–40% of adults [146]. Some adult studies have shown positive effects on liver biochemistry with minocycline [141] and metronidazole [28].

Immunosuppressive and immunomodulatory drugs have not proven to be beneficial. Infliximab [148], budesonide [149], azathioprine, calcineurin inhibitors, and mechanistic target of rapamycin are ineffective [150]. There is a case report of succesful treatment of a 13-year-old boy with PSC and undetermined colitis with a combination of a steroid, salazosulfapyridine, and probiotic [151].

Chronic cholangitis may require biliary stent placement, balloon stricture dilation, and/or sphincterotomy to relieve an obstruction with brush cytology for evaluation of cholangiocarcinoma [152].

Liver transplantation is indicated in end-stage liver disease with decompensated cirrhosis, hilar cholangiocarcinoma, intractable pruritus, and chronic cholangitis

refractory to biliary stenting and/or stricture dilatation. The disease could recur in the graft in up to 20%. The graft survival was better in patients who underwent pre-/peri-liver transplantation colectomy [153]. No medication has been proven to reduce the time from PSC diagnosis to liver transplant or the development of cholangiocarcinoma. Transaminases and γGT should be monitored at least annually in all UC patients, to screen for PSC and autoimmune hepatitis. Chronic elevation of liver enzymes in the presence of cholestasis should be investigated with ultrasound followed by MR-cholangiopancreatography (MRCP), in addition to liver biopsy when indicated [154].

10.7.1.2 Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is characterized by elevated serum transaminase levels, interface hepatitis on liver biopsy, increased levels of immunoglobulin G, and the presence of specific autoantibodies [155, 156]. AIH is five times less commonly associated with IBD than PSC [146].

There are two types of AIH. Autoimmune hepatitis type 1 is associated with positive antinuclear antibodies and/or smooth muscle antibodies (ANAs/SMAs—positive 1:20), while AIH type 2 is associated with postive antibodies to liver/kidney microsomal type 1 and/or anti-liver cytosol type 1 (positive 1:10) [155–157].

Clinical Presentation

The clinical symptoms of liver disease include jaundice, acute hepatitis, and nonspecific symptoms such as fatigue, nausea, abdominal pain, and arthralgia [157]. Liver biopsy is needed to confirm the diagnosis and to evaluate the severity of liver damage. AIH has characteristic histologic findings including dense portal tract inflammation, lobular activity, interface hepatitis, potential fibrosis [155, 156].

Treatment

Treatment of AIH should be started as soon as the diagnosis is made. The first-line treatment is prednisolone/prednisone (2 mg/kg/day, up to 60 mg/day), weaned down during 6–8 weeks to a maintenance dose of 5–7.5 mg/day, with monitoring of biochemical response alanine aminotransferase and aspartate aminotransferase [158]. In the presence of inadequate biochemical response to steroids after 4–6 weeks, azathioprine should be added (0.5 mg/kg/day gradually increased to 2–2.5 mg/kg/day) [158]. Budesonide is under investigation as alternative to prednisone for maintenance therapy. Second-line treatment options, if azathioprine fails to achieve normalization of liver function or is not tolerated, are mycophenolate mofetil, cyclosporine, and tacrolimus which should be administered only in specialized hepatology centers [158, 159].

Maintenance immunosuppressive treatment should continue for at least 2–3 years. The chances for successful withdrawal, however, remain between 20% and 40%. The patients after withdrawal of immunosuppression should continue to be monitored for AST/ALT/IgG/autoantibodies on a three-monthly basis for at least 5 years [158]. With appropriate treatment progression to end-stage liver disease is rare.

10.7.1.3 Autoimmune Sclerosing Cholangitis

Sclerosing cholangitis is a chronic inflammatory disorder that affects the intrahepatic and/or extrahepatic biliary tree leading to bile duct and liver fibrosis. The diagnosis is based on typical bile duct lesions being visualized on cholangiography [158]. Sclerosing cholangitis in children/adolescents is widely referred to as PSC, borrowing the adult definition. There are important differences, however, between adult PSC and juvenile sclerosing cholangitis [158]. ASC is an overlap syndrome between AIH (especially type 1) and PSC, occurring predominantly in children and young adults. IBD is more common in ASC (45%) than in AIH type 1 (20%) [160]. It has been suggested that the chronic IBD associated with ASC may represent a distinct nosologic entity, different from classic UC and CD, being characterized by right-sided colitis with frequent rectal sparing, and small bowel mucosal breaks on capsule enteroscopy [81].

Distinguishing factor between AIH and ASC is evidence of cholangiopathy and requires cholangiography [magnetic resonance colangiopancreatography (MRCP)] [158].

Virtually all ASC patients are seropositive for ANA and/or SMA. The difference between ASC amd AIH is in atypical p-ANCA antibodies which are more common in children with ASC than AIH type 1 (74% positivity, versus 45%), biliary disease on MRCP, and ductal involvement on the liver biopsy in ASC patients. There is a scoring system in distinguishing between AIH and ASC [158].

Treatment is based on the same immunosuppression as in AIH. Ursodeoxycholic acid (15–20 mg/kg/day) is often used to help with the biliary disease component, but as with PSC, it is unknown if this has any effect in slowing the progression of the disease.

Liver transplantation is needed in 10% of children with AIH and 20% with ASC [155].

The prognosis is worse in ASC compared to AIH

10.7.2 Thrombotic Disorders

Patients with inflammatory bowel disease are at increased risk of a first and recurrent venous thromboembolism (deep vein, especially thrombosis of the legs and pulmonary embolism, less common cerebral venous sinus thrombosis, hepatic, portal, and mesenteric vein thrombosis) [161, 162]. There is no increased risk of arterial thromboembolism (ischemic stroke, cardiac ischemia, peripheral vascular disease, and mesenteric ischemia) in IBD patients [162, 163]. The risk is much more prominent at the time of a flare [164] and in patients with extended disease (pancolitis in UC patients and extensive colonic involvement in CD) [165]. There is no significant difference linked to sex or the type of IBD [166].

In a Danish cohort study of venous thromboembolism in adults and children, patients with IBD had twice the incidence of deep venous thrombosis and pulmonary embolism as in the general population. Relative risks were particularly high at young ages, though actual incidence increased with age. Forty out of 5424 (0.7%) children with IBD had a venous thromboembolism [47].

10.7.2.1 Portal Vein Thrombosis

Recent abdominal and nonintestinal surgery, younger age, and female sex are associated with a higher incidence of portal vein thrombosis [162, 163].

Portal vein thrombosis may clinically present as an acute abdomen, chronic or insidious presentation. If the superior mesenteric vein is also occluded, then they may have nonbloody diarrhea and intermittent abdominal pain that can progress to possible bowel infarction, ascites, and hematochezia. Chronic portal vein thrombosis more commonly presents as an incidental finding on imaging or as a gastric or esophageal variceal bleed associated with portal hypertension [167, 168].

Diagnosis is made in most cases using color Doppler ultrasound, contrast-enhanced computerized tomography scanning, or magnetic resonance angiography [7].

In IBD patients with symptomatic acute splanchnic veint hrombosis (portal, mesenteric, and/or splenic vein thrombosis), it is recommended to use anticoagulant therapy. In patients with incidentally detected splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), the anticoagulation therapy is not recommended [169].

10.7.2.2 Venous Thromboembolism and Hepatic Vein Thrombosis (Budd-Chiari Syndrome)

Deep vein thrombosis and pulmonary embolism are the main thromboembolic complications and were observed in up to 90.4% of IBD patients with a history of venous thrombosis. Cerebral, portal, mesenteric, splenic, or internal jugular vein thrombosis represents only 9.6% of venous thrombotic events in patients with IBD [93].

Prophylaxis of venous thromboembolism in IBD starts with the prevention and treatment of thrombosis risk factors. Hydration, correction of deficiencies in vitamins (particularly in vitamins B6 and B12 and folate) that can reduce homocysteine levels, graduated compression stockings or pneumatic devices, and early mobilization after surgery should always be considered, especially in hospitalized IBD patients [170].

Pharmacological prophylaxis with anticoagulants in IBD patients is recommended by several practice guidelines for conditions associated with a higher risk of venous thromboembolism, particularly in hospitalized patients with active disease. Low-molecular-weight heparin and unfractionated heparin are recommended for thromboprophylaxis in IBD patients [169].

The treatment of venous thromboembolism in children with clinically inactive IBD who are diagnosed with their first episode of venous thromboembolism in the presence of an unrelated reversible provoking factor is with anticoagulant therapy for a minimum of 3 months. For pediatric patients with IBD diagnosed with their first episode of venous thromboembolism in the presence of active disease, it has been suggested that anticoagulant therapy should be continued until the IBD is in remission for at least 3 months [169].

10.8 Lung Involvement

Pleural and pericardial manifestations of IBD are uncommon. Pulmonary involvement in IBD is often latent or subclinical and may be detected solely by laboratory or imaging techniques. Inflammatory bowel disease can affect the lung parenchyma and airways. Very rare it involves the pleural space and pericardium, causing inflammatory exudative pleural or pericardial effusions [171]. Lung diseases can develop at any time in the course of IBD, but usually after the onset of the bowel disease; however, they may emerge after colectomy and cessation of therapy [172].

Thoracic serositis in patients with IBD can cause pleuritis, pericarditis, pleuropericarditis, or myopericarditis. It is important to evaluate the pleural effusion and rule out other etiologies before making this diagnosis. Pleural or pericardial biopsies are rarely necessary and probably show nonspecific acute and chronic inflammatory changes. Although the specific pathophysiology of pleuropericardial disease in patients with IBD remains unclear, the response to systemic steroids is usually adequate [173, 174]. The true prevalence of lung involvement in IBD remains unknown, and it seems rather variable, because in some series only a few cases of respiratory complications have been found [171]. Data on CD-related pulmonary disease in children are insufficient.

10.8.1 Pathogenesis

The colonic and respiratory epithelia share an embryonic origin from the primitive foregut and have columnar epithelia with goblet cells and submucosal mucus glands. The lungs and gastrointestinal tract contain submucosal lymphoid tissue and play crucial roles in host mucosal defense [172, 175]. The similarity in the mucosal immune system causes the same pathogenic changes that may result from epithelial exposure to common antigens by inhalation and ingestion, leading to sensitization of the lymphoid tissue and inflammation [176]. The activated inflammatory cells in the bowel tissues are capable of producing several circulating cytokines such as interleukin (IL)-1, IL-2, and IL-6 and tumor necrosis factor (TNF)-α. These and other mediators can regulate the endothelial cell adhesion molecules, alter leukocyte migration, increase production of damaging reactive oxygen metabolites, and induce damage of lung parenchyma [177, 178].

10.8.2 Airway Diseases

Airway involvement in IBD can develop from the trachea to the bronchioles [179–182].

Severe tracheal inflammation and obstruction are rare manifestations of IBD and correspond to the presence of irregularly friable and hemorrhagic tissue at

endoscopy [183]. The tracheal epithelium is often ulcerated and is replaced by a thin layer of fibrin [174]. Upper airway involvement comprises glottic/subglottic stenosis, tracheal inflammation, and stenosis [88–90]. The main symptoms are coughing, dyspnea, stridor, and hoarseness [184]. It can be identified by history, chest radiographs, computed tomography, and pulmonary function testing. Laryngoscopic evaluation is necessary because airway compromise can occur [174].

Large airway disease involves bronchial inflammation and suppuration. These are the most common manifestations of pulmonary involvement in IBD.

Bronchiectasis is the most commonly reported entity, and it is noted in 66% of cases of IBD involving the large airways [176]. The majority of patients with bronchiectasis have UC.

The second most common large airway disease in IBD is chronic bronchitis, which is distinguished from bronchiectasis only by the degree and extent of pulmonary abnormality, and further abnormalities include suppurative large airway disease and acute bronchitis [185]. The main symptom is chronic cough with purulent sputum poorly responsive to antibiotics [186]. Bronchial biopsy shows similar features: squamous cell metaplasia in the mucosa that is sometimes infiltrated by neutrophils and a dense cuff of lymphocytes and plasma cells infiltrating the submucosa [187].

Small airway disease is less frequent and was described separate from large airway disease. These abnormalities seem to occur earlier in the course of the disease and at a younger age than large airway disease [182, 188–191]. Chest high-resolution computed tomography shows bronchiolar wall thickening, mucoid impaction, centrilobular ground-glass nodules, and mosaic attenuation because of air trapping, and some patients have normal pulmonary function test (PFT) findings [192].

Bronchiolitis is the most commonly reported disease involving the small airways in patients with IBD. Bronchiolitis in specific settings leads to bronchiolectasis, resulting in bronchiectasis. The respiratory alteration presented with nonproductive cough, progressive dyspnea, and chest pain. Histological samples from the open lung biopsy reveal fibrosing and stenosing bronchiolitis and inflammatory lesions [188, 193, 194]. Steroids are the major therapy although some patients do not require systemic therapy.

10.8.3 Lung Parenchymal Diseases

In contrast to other EIM, lung parenchymal disease associated with IBD is seen more commonly with UC than CD [187]. Age of onset varies, and there is a slight female predominance.

Bronchiolitis obliterans organizing pneumonia is the most commonly reported parenchymal manifestation of IBD [195, 196]. Bronchiolitis obliterans organizing pneumonia is often caused by inhalation injury or results from a postinfection origin or drugs and may present acutely or subacutely with fever, cough, dyspnea, and pleuritic chest pain [197, 198]. Dyspnea and cough are the most common presenting symptoms. Systemic steroids are recommended and effective for treatment of this complication [197].

Other forms of parenchymal disease that may be related to IBD or drug toxicity are eosinophilic pneumonia and nonspecific interstitial pneumonitis [174].

In patients with IBD, pulmonary nodules have been infrequently reported, which histologically appear to be necrobiotic (composed of sterile aggregates of neutrophils with necrosis), granulomatous, or otherwise [199]. Important is to distinquish an infectious origin, because necrobiotic nodules respond to steroids but not to antibiotics [174].

The manifestations of lung parenchymal disease in IBD usually respond dramatically to inhaled or systemic steroids. The addition of cyclophosphamide or anti-TNFα drug (e.g., infliximab, adalimumab) may show rapid clinical and radiological response and are well tolerated [200, 201].

10.8.4 Pleural Diseases

IBD involves the pleural space and pericardium and in rare cases causes inflammatory exudative pleural and/or pericardial effusions [202, 203]. Pleuropericardial inflammatory disease and effusion can be directly related to IBD, its complications, associated infections, or the medications used to treat IBD [204]. Pleural diseases can be classified as pneumothorax [205], pleural thickening, pleuritis, and pleural effusion [206].

Pleural fluid collection is usually unilateral, an exudate with neutrophils, and may be hemorrhagic. It is important to evaluate pleural effusion and rule out other etiologies before making this diagnosis. Mesalazine may also induce lupus-like symptoms, such as arthralgia, pericarditis, tamponade, and/or pleural effusion, with positive antinuclear antibody [174].

Pleural effusion associated with IBD is effectively treated with systemic steroids; however, pleural drainage may be required occasionally.

10.8.5 Enteric-Pulmonary Fistulas

Enteric-pulmonary fistulas such as colobronchial [207–210], ileobronchial [210], and esophagobronchial [211] fistulas are rare complications of IBD. Fistula formation occurs more frequently in CD and [212] develops primarily in the perineal area [212]. In most cases, colobronchial fistulas extend from the splenic flexure in the colon to the lower lobe of the left lung. This is likely due to the anatomical proximity between the two structures [174].

Recurrent pneumonia with feculent sputum in patients with CD should raise suspicion of colobronchial fistula. Once the abnormal connections between the bowel and respiratory tract are suspected, an enema using water-soluble contrast medium helps to confirm the presence of fistulas [208]. Colopleural fistula and fecopneumothorax are rare but life-threatening complications of CD. Surgical treatment is mandatory as soon as the diagnosis is established [213].

10.8.6 Pulmonary Function Test Abnormalities

Pulmonary function test abnormalities are found frequently in adult patients with IBD without presence of any respiratory symptoms and lung radiograph findings [174]. Functional and structural pulmonary involvement in children with IBD is qute uncommon.

Various studies testing pulmonary function in patients with IBD have revealed a spectrum of abnormalities including restrictive disease, obstructive disease, bronchial hyperresponsiveness and hyperinflation as, well as a decreased diffusion capacity of the lung [214].

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Castleman Disease

11

Dale M. Kobrin and David C. Fajgenbaum

11.1 Introduction

Castleman disease (CD) refers to a group of rare immunologic disorders defined by a spectrum of characteristic histopathologic features present in enlarged lymph nodes. Patients across the CD spectrum often exhibit fevers and other constitutional symptoms throughout their disease course. Dr. Benjamin Castleman first described the disease in 1954 [1] and then subsequently published a case series of 13 patients in 1956 [2]. In this initial case series, the solitary masses were found to be hyperplastic lymph nodes with similar histopathologic features across patients, including hyperplastic lymphoid follicles and marked capillary proliferation. These patients were largely asymptomatic, lacked significant laboratory abnormalities, and had a common pattern of histopathologic features [2].

Over time, patients with multiple regions of enlarged lymph nodes that demonstrated histopathological changes consistent with the CD spectrum were reported [3]. These "multicentric" CD (MCD) cases experienced more severe clinical and laboratory abnormalities, such as constitutional symptoms, cytopenias, and severe organ dysfunction, due to a cytokine storm often including interleukin-6 (IL-6) [4]. These cases have worse outcomes than the localized or "unicentric" CD (UCD) cases and require different treatments [5]. It has also become clear that CD-like histopathologic lymph node features are not specific to Castleman disease and can

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Table 11.1 Castleman disease mimics

Autoimmune	Malignancy	Infectious
Systemic lupus erythematosus	Lymphoma	Human immunodeficiency virus
Rheumatoid arthritis	Follicular dendritic cell sarcoma	Epstein-Barr virus
Adult-onset still disease	Multiple myeloma	Cytomegalovirus
Juvenile idiopathic arthritis		Toxoplasmosis
Autoimmune lymphoproliferative syndrome		Tuberculosis

be seen in a number of malignancies and autoimmune diseases [6]. Thus, it is essential that CD be appropriately classified into subtypes and that diagnostic criteria exclude histopathologic mimics (Table 11.1).

11.2 Classification

CD is first divided based on the number of regions of enlarged lymph nodes with characteristic histopathological changes. UCD often presents with a single enlarged lymph node but may present with multiple enlarged lymph nodes in a *single* region of the body [7]. In MCD, enlarged lymph nodes must be present in multiple regions of the body.

UCD is not further divided into clinical subtypes, as there are no features that have a material impact on treatment or prognosis. However, MCD is further classified into subtypes based on known and suspected etiologies, which have significant implications for treatment and prognosis. Human herpes virus-8 (HHV-8)-associated MCD is caused by uncontrolled Kaposi sarcoma-associated herpesvirus (KSHV)/human herpesvirus-8 (HHV-8)) infection [8] while MCD diagnosed in patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome (POEMS-associated MCD) is thought to be caused by cytokine production by the monoclonal plasma cells underlying the coexisting POEMS syndrome [9]. The remainder of MCD cases fall into the heterogeneous "idiopathic MCD" (iMCD category. Within iMCD, at least one distinct clinical subtype has been described, which involves thrombocytopenia, anasarca, fever/myelofibrosis, renal dysfunction, organomegaly, and normal or mildly elevated gamma globulin levels. This subtype is referred to as iMCD -thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly (TAFRO) and seems to demonstrate a more severe clinical course [4]. The remainder of iMCD cases, which often demonstrate thrombocytosis and severe hypergammaglobulinemia, are referred to as iMCD not otherwise specified (iMCD-NOS) [10].

This chapter will provide a summary of the clinical features and pathogenesis of the various subtypes of CD (Fig. 11.1).

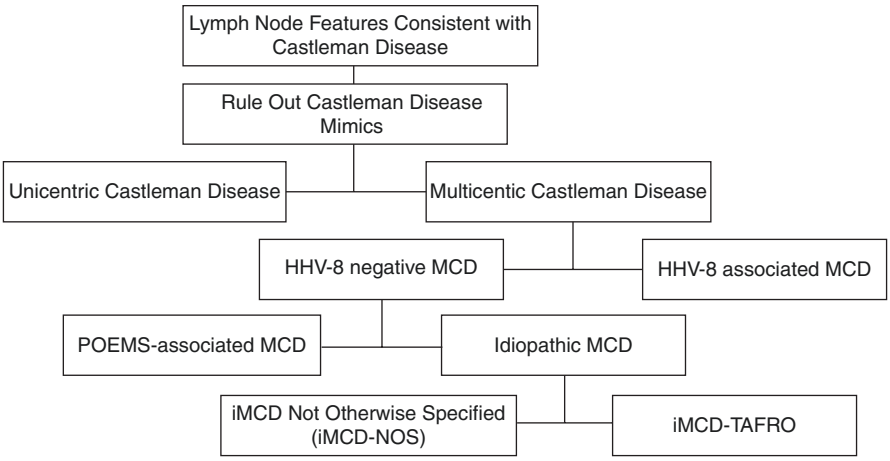

Fig. 11.1 Castleman disease classification

11.2.1 Unicentric Castleman Disease

11.2.1.1 Clinical Features and Management

Diagnosis of UCD requires enlarged lymph nodes to be contained to a single lymph node region, histopathologic features consistent with CD on biopsy of an enlarged lymph node, and the exclusion of histopathologic mimics; no abnormal clinical or laboratory parameters are needed [7]. Histopathology of UCD is more commonly the hyaline vascular pattern, but plasmacytic and mixed histopathological subtypes can also be seen (see Sect. 11.2.2 for descriptions of histopathology) [11].

UCD patients are commonly asymptomatic with normal laboratory testing. Enlarged lymph nodes in UCD can be found anywhere in the body and may be incidentally discovered by unrelated imaging studies [11]. When UCD patients do report symptoms, they may be due to compression of local structures by the enlarged lymph node (e.g., pain or pressure in the chest or abdomen, shortness of breath, or urinary obstruction) or due to systemic cytokine production [11]. Systemic inflammatory signs and symptoms, such as constitutional symptoms, extravascular fluid accumulation, and laboratory abnormalities, can be seen in UCD; however, they are more commonly seen in MCD (see Sect. 11.2.2) [12]. Of note, paraneoplastic pemphigus, a life-threatening autoimmune blistering disorder, is sometimes associated with UCD and can present prior to the diagnosis of UCD [13]. UCD patients generally have a good prognosis, but may suffer severe complications. In particular, paraneoplastic pemphigus and follicular dendritic cell (FDC) sarcoma are the two most frequently observed life-limiting sequelae of UCD based on anecdotal report [14].

Surgical removal of the enlarged node or region of nodes is the treatment of choice for UCD. Complete surgical excision in UCD is almost always curative and almost always induces a complete remission of symptoms and laboratory

abnormalities associated with the disease [15]. According to anecdotal report, patients with unresectable UCD due to neighboring vital structures are often given medications used for MCD with variable success. Recurrences of UCD after complete excision are very uncommon but have been reported [5]. As a result, it is thought that the pathological cell types in UCD are contained in the excised lymph node. No cases of UCD have ever been reported to transition into MCD.

11.2.1.2 Pathogenesis

Proposed mechanisms for UCD include viral, neoplastic, and reactive inflammatory processes. No mechanism has been exhaustively investigated, but current evidence best supports a neoplastic process.

The strongest support for a neoplastic process comes from a study done by Chang et al. [16] on female UCD patients, which used a human androgen receptor gene (HUMARA) assay to demonstrate monoclonality in the lymphoid tissue of 19 of 25 UCD patients and 0 of 20 control cases of lymphoid hyperplasia. Testing for T and B cell monoclonality in this sample was negative, leading the authors to speculate that the monoclonal cell population was likely stromal in origin [16]. Additional support for a neoplastic process comes from several case reports describing cytogenetic anomalies in cultured lymph node stromal cells [17–20] and a case series of 11 UCD patients, which demonstrated mutations in known cancer-causing genes in two of nine cases that underwent next-generation sequencing [21]. Furthermore, UCD is associated with paraneoplastic pemphigus, which commonly occurs secondary to non-Hodgkin lymphoma and other hematologic neoplasia [22]. Rare reports of UCD running in families do exist, but genetic sequencing on these cases has not been performed [23, 24].

Despite evidence of a neoplastic process in UCD, the underlying cell type driving UCD pathogenesis has not been conclusively demonstrated. The previously described studies suggest that the neoplastic cells driving UCD are stromal cells, specifically FDCs, rather than lymphocytes [16, 17, 19, 20]. This is supported by commonly seen histopathologic lymph node features in UCD—such as stromal cell overgrowth, FDC prominence, and FDC dysplasia—and reports of patients developing FDC sarcoma in a region of lymph nodes previously harboring UCD [25–27]. FDCs are involved in germinal center formation, directing lymphocyte migration within lymph nodes, and promoting B cell survival; disruption of these functions may underlie the pathogenesis and histopathologic features of UCD [28].

Identifying effector cytokines has been an active research focus in MCD, as a cytokine storm is thought to be responsible for the constitutional symptoms and organ dysfunction present in the disease. While systematic investigation of effector cytokines has not been performed in UCD, it is suspected that similar effector cytokines to those involved in MCD are involved in the small portion of UCD cases with constitutional symptoms and organ dysfunction. In particular, IL-6 is likely to be involved based on case report data [29]; however, it is unclear if IL-6 plays a role in cases of UCD that present without symptoms and organ dysfunction. Interestingly, FDCs' role in coordinating migration of lymphocytes is largely mediated through secretion of chemokine ligand (C-X-C motif) 13 (CXCL13). Dysplastic FDCs in UCD lymph nodes strongly

express this chemokine [27], and proteomics data in iMCD patients found that CXCL13 was the most significantly upregulated cytokine during disease flares [30]. Unfortunately, CXCL13 levels have not been systematically studied in UCD.

Although significant work is still needed to determine the etiology and pathogenesis of UCD, research to date supports a clonal proliferation of FDCs, likely due to acquired mutations, as the etiological driver of the disease.

11.2.2 Multicentric Castleman Disease

Although UCD and MCD share common histopathological features, the diseases differ significantly in clinical presentation, treatments, and outcomes. Diagnosis of the different MCD subtypes requires enlarged lymph nodes in multiple lymph node regions, histopathologic findings compatible with Castleman disease, and exclusion of histopathologic mimics; full consensus diagnostic criteria have been established only for iMCD [6]. The iMCD diagnostic criteria define a histopathological spectrum ranging from hypervascular (similar to the previously described hyaline vascular variant observed in UCD) to plasmacytic. Hypervascular histopathological features include regressed germinal centers, FDC prominence, hypervascularization, and expanded mantle zones with cells organized in a concentric "onion skinning" appearance. Plasmacytic histopathological features include sheet-like plasmacytosis and increased numbers of follicles with large hyperplastic germinal centers. A "mixed" pattern containing histopathologic features of both hypervascular and plasmacytic also exists [6].

Regardless of subtype, MCD patients typically present with constitutional symptoms, such as fever, fatigue, and weight loss; lymphadenopathy and organomegaly; extravascular fluid accumulation; and laboratory abnormalities, including anemia, thrombocytosis or thrombocytopenia, elevated ESR and CRP, hypergammaglobulinemia, and hypoalbuminemia [12]. As noted earlier, MCD is categorized into subtypes based on known etiologic drivers and treatment approaches. While the above features are often found across MCD subtypes, there are also unique clinical features and aspects of pathogenesis that will be discussed for each subtype later.

11.2.2.1 Human herpes virus-8-Associated Multicentric Castleman Disease

Uncontrolled infection with HHV-8 is the well-established etiology of HHV-8-associated MCD [31]. HHV-8 infection was first associated with MCD in 1994, and following this discovery [32], the MCD research field shifted focus toward this subtype. As a result, the etiology and pathogenesis of HHV-8-associated MCD are better understood than other subtypes of CD.

HHV-8-associated MCD is most commonly diagnosed in human immunodeficiency virus (HIV)-positive patients but is also seen in patients with other forms of immunodeficiency [33]. HHV-8-associated MCD is often associated with other disorders caused by the HHV-8 virus, such as Kaposi sarcoma [34]. Consensus diagnostic criteria for HHV-8-associated MCD have not been established, but diagnosis

of the disease is commonly based on compatible clinical presentation, lymph node biopsy demonstrating histopathologic features consistent with CD, and detection of the HHV-8 virus either by lymph node immunohistochemical staining for latency-associated nuclear antigen-1 (LANA-1) or by HHV-8 polymerase chain reaction (PCR) of peripheral blood samples during disease flare. Unlike other subtypes of Castleman disease, which may demonstrate hypervascular, plasmacytic, or mixed pattern of histopathologic features, HHV-8-associated MCD is only associated with a plasmablastic histopathologic pattern [35]. This plasmablastic pattern is similar to the plasmacytic pattern seen in other subtypes of CD but includes increased numbers of plasmablasts in the outer mantle zones of follicles [35].

The HHV-8 virus primarily infects B cells and plasmablasts. When HHV-8 escapes from host immune control, it is able to lytically replicate in lymph node plasmablasts and signal for the release of cytokines that drive clinical and pathological symptoms [33, 36]. The critical role of B cells in HHV-8-associated MCD is evidenced by the high success rate of treatment with rituximab, a B-cell–depleting therapy [37]. In addition to B cells, the role of peripheral T cells, including polyfunctional effector memory $CD8^+$ T cells, has also been explored and may be associated with the pathogenesis of HHV-8-associated MCD [38].

Viral infection of host immune cells by HHV-8 causes a number of disruptions to normal biologic pathways and cytokine production leading to B-cell and plasma cell proliferation, angiogenesis, and an acute-phase reaction [39]. Latently expressed viral-FLICE inhibitory protein (vFLIP) upregulates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) leading to increased production of human IL-6 [40], while a viral G-protein-coupled receptor may lead to the upregulation of vascular endothelial growth factor (VEGF) and other factors implicated in HHV-8-associated MCD pathogenesis [39, 41]. In addition to increasing levels of hIL-6, HHV-8 also drives pathogenesis through a viral variant of the cytokine IL-6 (vIL-6) [42]. Human IL-6 operates through the IL-6 receptor (IL-6R) and gp130, a transmembrane protein that forms a complex with IL-6 and IL-6R, leading to downstream signaling [43]. Unlike human IL-6, which must bind to membrane-bound or serum IL-6R in order to form a functional complex with gp130, vIL-6 can complex with gp130 without IL-6R. As a result, vIL-6 is able to activate cells that express only gp130 rather than gp130 and membrane-bound IL-6R [44]. Consequently, it is possible that vIL-6 effects are present in a wider range of cell types than human IL-6.

11.2.2.2 Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Plasma Cell Disorder, and Skin Changes-Associated Multicentric Castleman Disease

Compared to HHV-8-associated MCD, HHV-8-negative MCD subtypes such as POEMS-associated MCD and iMCD have historically received less research attention, despite epidemiologic data suggesting that HHV-8-negative MCD subtypes have similar, if not greater, incidence than HHV-8-associated MCD [4]. While the etiology of most cases of HHV-8-negative MCD is not known, in patients presenting with MCD and concurrent POEMS syndrome, both diseases are thought to be driven by a population of monoclonal plasma cells. Case series estimate

POEMS-associated MCD to be present in approximately 15% of patients with POEMS syndrome [45]. Interestingly, patients with POEMS-associated MCD have been reported to have evidence of previous exposure to HHV-8 by viral serology and PCR of tissue [46]; however, positive LANA-1 lymph node staining, which would suggest a pathogenic role of the virus, has not been reported in POEMS-associated MCD.

The pathophysiology of POEMS syndrome and POEMS-associated MCD is unclear, but increased levels of cytokines secreted by monoclonal plasma cells are thought to drive both diseases. VEGF is the cytokine that best correlates with POEMS syndrome acuity [47]; however, mixed results with VEGF blockade suggest that additional cytokines are involved [48]. Other cytokines implicated in POEMS syndrome include IL-6, IL-12, transforming growth factor (TGF)-1β, and tumor necrosis factor (TNF)-α [49]. The cells responsible for producing these particular cytokines have not been definitively identified, but monoclonal plasma cells that have undergone genomic events are suspected. Highlighting the primary role of the monoclonal plasma cell population in POEMS pathogenesis, radiation to an isolated plasmacytoma is often curative [9].

11.2.2.3 Idiopathic Multicentric Castleman Disease (Idiopathic Multicentric Castleman Disease and Idiopathic Multicentric Castleman Disease-Thrombocytopenia, Anasarca, Fever, Reticulin Fibrosis, and Organomegaly)

The iMCD subtype of CD is idiopathic, and is associated with a variety of clinical and histopathologic features. It is divided into at least two distinct subtypes based on clinical findings, iMCD-TAFRO and iMCD-not otherwise specified (iMCD-NOS).

Patients with iMCD-NOS often present similarly to POEMS-associated MCD, whereas patients with iMCD-TAFRO present with more severe disease characterized by thrombocytopenia (as opposed to thrombocytosis), anasarca, fever/reticulin fibrosis on bone marrow biopsy, renal dysfunction, and organomegaly [10]. Patients with iMCD-TAFRO typically have normal or mildly elevated gammaglobulins (as opposed to the higher levels of gammaglobulins seen in iMCD-NOS and POEMS-associated MCD) [4]. iMCD-TAFRO patients can suffer acute, rapidly progressive multisystem organ failure and frequently require support in an intensive care unit.

Although the etiology of iMCD remains unknown, the clinical manifestations of the disease are thought to be caused by elevated cytokines such as IL-6, which appears to be a primary driver of iMCD in some patients. However, the heterogeneity of the disease and inconsistent response to specific treatments, including anti-IL-6 therapies, suggest that dysregulation of multiple immune processes may be involved [50]. The CD research community, led by the Castleman Disease Collaborative Network (CDCN), has focused on four hypothesized candidate etiologic drivers of iMCD pathogenesis.

Etiology: Autoimmune Hypothesis

An autoimmune process involving self-reactive antibodies or T cells may drive iMCD. Support for an autoimmune etiology includes overlapping clinical and

histopathological features between iMCD and known autoimmune diseases. Nearly all lymph node biopsies from patients with rheumatoid arthritis and 15–30% of those from patients with systemic lupus erythematosus display CD-like histopathological features [51, 52]. Furthermore, approximately 30% of reported cases of iMCD have auto-antibodies or autoimmune hemolytic anemia [4]. It is unclear if autoantibodies and autoimmunity in iMCD are etiologic drivers, propagators of inflammation, or arise secondary to another process.

Etiology: Autoinflammatory Hypothesis

iMCD may be caused by abnormal immune activation and regulation due to germline mutations in genes regulating inflammation. A number of interesting observations support this hypothesis, but no large series demonstrating common mutations specific to iMCD have been reported. Homozygous mutations in Cat eye syndrome critical region protein 1 (CECR1), encoding for adenosine deaminase 2, ADA2, which may lead to increased IL-6 activity through a deficiency of ADA2, were described in a child with an MCD-like syndrome [53, 54]. Additionally, in a study performed by Stone et al. [55] on iMCD patients and healthy controls, iMCD patients were somewhat more likely (49% vs. 33%) to harbor a polymorphism in the IL-6R gene. Measured levels of soluble IL-6R (sIL-6R) were significantly higher in individuals with this polymorphism, either with or without iMCD, which may contribute to increased IL-6 activity through a trans-signaling pathway [55]. Further research is needed to explore these findings and delineate their roles in iMCD pathogenesis.

Etiology: Neoplastic Hypothesis

A neoplastic cell population that has acquired oncogenic mutations may drive iMCD pathogenesis. Such a process is suggested by the significant clinical and histopathologic overlap between iMCD and lymphoma as well as iMCD patients' increased rate of malignancy compared to age-matched controls [4]. A small study of iMCD patients found monoclonality in the lymph nodes of four out of four cases [16]. Similar to UCD, it is thought that these monoclonal cells were stromal in origin, as this study and others found lymphocytes to be polyclonal [56]. Recently, next-generation sequencing of 405 cancer genes identified a somatic DNA (cytosine-5)-methyltransferase 3A—DNMT3A (L295Q) mutation in the lymph node tissue of an iMCD-TAFRO patient [57]. While this result is promising, further research is needed to explore the role of this mutation in iMCD pathogenesis.

Etiology: Pathogen Hypothesis

Lastly, iMCD has significant clinical and histopathologic overlap with HHV-8-associated MCD, suggesting that iMCD may be due to previously undetected HHV-8 infection, infection with a different known pathogen, or infection with a novel pathogen. Several cases have reported evidence of infectious pathogens present in iMCD patient samples, including Epstein-Barr virus (EBV), HHV-6, hepatitis B virus, *cytomegalovirus*, toxoplasma, and *Mycobacterium tuberculosis* [58–63]. To test all aspects of the pathogen hypothesis, a recent study used VirCapSeq [64] technology to look for pathogens in iMCD and UCD cases compared to

HHV-8-associated MCD and lymphoma controls. No evidence of HHV-8 infection or novel pathogens was discovered in the iMCD cases; however, Herpesviridae and non-Herpesviridae viruses were inconsistently present in iMCD cases [65]. It is unclear if these infections are involved in iMCD pathogenesis.

Dysregulated Cell Types

Research into iMCD has also sought to identify cell types responsible for driving iMCD pathogenesis. T cells, B cells, plasma cells, monocytes, endothelial cells, and FDCs have been suspected of driving iMCD pathogenesis and/or producing IL-6 [66–70]. Although reports have been inconsistent, evidence for a pathogenic role of B cells in some patients does exist. Proliferation and secretion of autoantibodies by $CD5^+$ mantle zone B cell in HIV-negative (HHV-8-unknown) MCD cases and successful treatment of a subset of iMCD patients with B-cell depletion with rituximab support a role for B cells in disease pathogenesis [4, 25]. However, many patients do not respond to rituximab, suggesting other cell types must also be involved [4]. Evidence implicating T cells comes from a review reporting elevated serum soluble IL-2 receptor (sIL2R), which is shed by activated T cells, in 20 of 21 published cases of iMCD; furthermore, iMCD patients have responded to treatment with cyclosporine and sirolimus, immunosuppressants thought to target T cells [4].

Effector Cytokines and Signaling Pathways

A number of cytokines have been implicated in iMCD pathogenesis, particularly IL-6, which was first associated with iMCD in 1989 [69]. IL-6 is the established driver of iMCD pathogenesis in a subset of patients and is important for a number of immune system functions and clinical features observed in iMCD, including increased VEGF secretion, B-cell and plasma-cell maturation, plasmacytosis, hypergammaglobulinemia, and thrombocytosis [31]. Hyper-IL-6-secreting mouse models demonstrate an iMCD-like syndrome, and anti-IL-6 therapy is an effective treatment for these mice [71, 72]. In iMCD patients, symptoms have been shown to be correlated with IL-6 levels [73]; the administration of recombinant IL-6 to cancer patients in a phase I–II trial resulted in iMCD-like clinical features [74]; and treatment with siltuximab, an anti-IL6 monoclonal antibody, is effective in approximately one-third of iMCD patients [75].

While siltuximab is the only Food and Drug Administration (FDA)-approved therapy for iMCD, a significant proportion of patients fail to respond to the drug, suggesting that other cytokines are likely to be involved in the pathogenesis of these cases. Recent serum proteomic analysis of iMCD patients has identified several cytokines of interest beyond IL-6. In a study by Iwaki et al. in 2017 , of 16 iMCD patients in flare (11 iMCD-TAFRO and five iMCD-NOS) and 21 healthy controls, there was no statistical difference in IL-6 levels across all three groups. Significant elevations were found in several of the other cytokines assayed, including IL-10, IL-23, and VEGF, which were elevated in both iMCD groups relative to controls, and CXCL10, which was significantly elevated in the iMCD-TAFRO subjects relative to both the iMCD-NOS and healthy control groups [76]. VEGF is of particular interest, as a systematic review of iMCD case reports found elevated VEGF in 16 of 20 cases [4]. Furthermore, elevated VEGF levels may play a role in the capillary

leak syndrome, eruptive cherry hemangiomatosis, and lymph node hypervascularity observed in some iMCD cases [77].

Building on prior proteomics work, Pierson et al. recently performed systematic analysis of 1129 serum analytes in six iMCD patients using paired flare and remission samples. This study found that cytokine and chemokine signaling were the most upregulated pathways during disease flares, with significantly more upregulated chemokines than interleukins and other cytokines. CXCL13 (B lymphocyte chemoattractant) was found to be the most upregulated cytokine across all patients in flare, and lymph node CXCL13 immunohistochemistry demonstrated increased germinal center staining in a mesh-like pattern in iMCD subjects compared to controls. This mesh-like pattern of germinal center staining may represent FDCs, which produce CXCL13 to attract B cells to germinal centers as part of B cell maturation [30].

Serum proteomics has also helped to identify intracellular signaling pathways potentially involved in iMCD, with the mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathways being enriched among the most up and downregulated plasma proteins during iMCD flares [30]. Of particular interest for treatment, many of the compounds expected to counteract the most upregulated proteins observed in iMCD target PI3K and/or mTOR. A role for the PI3K/Akt/mTOR pathway in iMCD pathogenesis and its potential as a therapeutic target is suggested by a case report of a treatment refractory iMCD-TAFRO patient who has experienced prolonged remission with the mTOR inhibitor sirolimus [78]. Additional work is needed to uncover the etiology and pathogenesis of iMCD and to identify effective treatments for siltuximab-refractory patients.

11.2.3 Future Directions

This chapter presents our current understanding of the clinical features and pathogenesis for each subtype of CD as of 2018. CD is a poorly understood inflammatory disorder that can often present with fevers and other systemic symptoms. We anticipate significant progress to be made thanks to the pipeline of research studies being led by the CDCN (www.cdcn.org/research-pipeline), including the ACCELERATE Natural History Registry (www.CDCN.org/ACCELERATE), which is open for patient self-enrollment.

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Mevalonate Kinase Deficiency

12

Brigitte Bader-Meunier

Mevalonate kinase deficiency is a rare autosomal recessive autoinflammatory disease caused by loss-of-function mutations in the mevalonate kinase (*MVK*) gene. It consists of an inborn error of cholesterol biosynthesis and comprises a continuous spectrum of clinical manifestations ranging from recurring febrile attacks associated with inflammatory symptoms, known as hyperimmunoglobulinemia D syndrome (HIDS; MIM 260920), to a more severe form, known as mevalonic aciduria (MVA; MIM 251170), presenting with psychomotor retardation, facial dysmorphia, cataract, and failure to thrive in addition to these febrile episodes [1]. Considering that serum levels of immunoglobulin D are not always increased in these diseases, the name "mevalonate kinase deficiency (MKD)" should now be preferred to "HIDS."

12.1 Pathogenesis

Mevalonate kinase deficiency (MKD) results from loss-of-function mutations in the *MVK* gene [2]. The encoded protein mevalonate kinase (MVK) is a key enzyme in the mevalonate pathway, producing cholesterol and a number of nonsterol isoprenoids, including geranylgeranyl pyrophosphate. The deficiency of mevalonate kinase results in the depletion of geranylgeranyl pyrophosphate, which has been reported to induce IL-1β release in myeloid cells [3]. Furthermore, it has been demonstrated that the depletion in geranylgeranyl pyrophosphate leads to RhoA inactivation, which induces pyrin inflammasome activation [4]. Thus, the role of the pyrin inflammasome is essential in the pathogenesis of MKD and results in a constitutive IL-1β

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release from peripheral blood mononuclear cells patients. IL1β is a potent inflammatory cytokine that is produced in a two-step process: induction of pro-IL1B and activation of the inflammasome, which is necessary for the conversion of pro-caspase-1 to caspase-1 that cleaves pro-IL1β into its mature form. The increased production of interleukin-1β in patients with MKD represents a putative link between mevalonate kinase deficiency and inflammation [5].

12.2 Clinical Manifestations

The main clinical characteristics of febrile attacks have been reported in three large series of HIDS patients [6–8]. The majority of reported patients are European or of European ancestry with the largest cluster in the Netherlands and Western Europe. However, MKD may also occur in patients from Arab descent [7]. The median age at disease onset is about 6 months, and MKD manifests usually within the first 2 years of life. Hydrops fetalis may be the revealing manifestation in neonates [9]. Attacks usually last 4–7 days and are often precipitated by vaccination, infections, minor physical trauma, or stress. Fever is mostly recurrent but may be also continuous in the most severe forms of the disease. Lymphadenopathy (generalized enlargement, cervical lymphadenopathy sometimes painful), mucocutaneous (aphthous stomatitis, exudative pharyngitis, maculopapular, erythematous nodules, or urticarial rash), gastrointestinal (GI) (abdominal pain, diarrhea, and vomiting), and joint (arthralgia, arthritis, and myalgia) symptoms are some more common manifestations during febrile attacks. Skin biopsy may show mild features of vasculitis, and nonspecific findings such as Sweet-like or cellulitis-like features. Neurological (headaches, irritability, cerebellar syndrome, mental retardation, or aseptic meningitis) and ocular involvement (uveitis, conjunctivitis, and cataract), hepatomegaly, splenomegaly, and pericarditis may also occur. Some additional severe manifestations are also reported. Severe GI manifestations consist in aseptic peritonitis, gastrointestinal bleeding, intestinal occlusion, gut perforation, abdominal adhesions, gastrointestinal ulcers, and perianal ulcers. MKD was also described in two patients with neonatal-onset severe ulcerative colitis and in older children or adults presenting with inflammatory bowel disease [7, 10]. Thus, IBD-like symptoms seem to be part of the clinical phenotype of MKD. Severe musculoskeletal manifestations comprise flexion contractures, bone deformity, bone erosion, persistent arthritis, osteitis, or osteolytic lesions [7, 8]. Fatal ischemic stroke and cerebral hemorrhage of unknown origin were also reported in adults [6, 11]. Retinitis pigmentosa has been described previously as a rare and severe complication of MKD. In a large cohort of adults with isolated retinitis pigmentosa, three patients had homozygous mutations in the *MVK* gene [12]. However, two of these patients reported recurrent febrile episodes during childhood and had current mild symptoms that could be related to MKD. Finally, MKD may be complicated by a macrophage activation syndrome [7, 8, 13], a life-threatening complication requiring an urgent treatment.

MKD leads to chronic involvement in a few patients: cholestatic liver disease [7, 14], dyserythropoiesis [14], glomerular disease (crescentic glomerulonephritis and

membranoproliferative nephritis) [7], interstitial pneumonitis [7], and chronic polyarthritis [15]. The reports of severe and/or recurrent bacterial infections, especially pneumococcal infections in the French series [7], of death of one patient among the cohort of van der Hilst et al. due to pneumococcal sepsis [6], and of recurrent pneumonia and fatal meningococcal sepsis in two out of 15 MKD Italian patients [16] support a possible link between MKD and immunodeficiencies. The mevalonate pathway is essential for the survival of *Streptococcus pneumoniae* in the lungs and serum, and the increase in mevalonate content of plasma resulting from MKD might favor the persistence of *S. pneumoniae* in patients with MKD. As a result, from these findings, immunization against *Streptococcus pneumoniae* has to be strongly recommended in patients with MKD.

12.3 Diagnosis

During febrile attacks, nonspecific elevated white blood cell (WBC) count, C-reactive protein (CRP) concentrations, and erythrocyte sedimentation rate (ESR) were reported. Immunoglobulin A level is also often elevated. Urinary mevalonic acid levels are increased during febrile attacks in most of the patients with MKD and generally correlate with disease severity. MKD seems very unlikely in patients with normal mevalonic acid excretion, but it cannot be excluded completely [17]. However, given the possibility of false-negative results (due to inherent variation in the sensitivity of different assay methodologies), experts concluded that detection of urinary mevalonic acid is not mandatory before genetic testing [18]. The diagnostic value of IgD was assessed in a prospective cohort of patients with recurrent fever and symptoms suggestive of MKD and was found to be disappointing: sensitivity 79%, specificity 27%, positive predictive value 50%, and negative predictive value 58% [19]. Thus, serum IgD is not a reliable diagnostic marker for MKD and therefore should not be used to determine the need for genetic testing for MVK mutations [18]. In all the cases, genetic testing for *MVK* mutation must confirm the diagnosis of MKD. The Infevers database (http://fmf.igh.cnrs.fr/infevers/) was established in 2002 to provide investigators with access to a central source of information about all sequence variants associated with genes connected with autoinflammatory diseases (AID). An experts' consensus was obtained in 2018 on the clinical significance of *MVK* gene variants [20]. p.Val377Ile is the most frequent mutation [6–8]. There is no clear correlation between genotype and phenotype [7].

12.4 Treatment

The objectives of treatment of the AID are to control the disease activity early and rapidly, to prevent any disease- and treatment-related damage, to enable participation in daily activities, and to improve health-related quality of life [18]. Management of patients with AID should ideally be guided by a multidisciplinary team in a tertiary center with expertise in AID, with access to genetic counseling.

Recommendations for the management of patients with MKD have been published in 2015 [18].

Nonsteroidal anti-inflammatory drugs (NSAIDs) may provide symptom relief during inflammatory attacks. Short-term glucocorticoids, with or without NSAIDs, may be effective for alleviating inflammatory attacks in mild MKD. On-demand IL-1 blockade by anakinra may be effective for decreasing the duration and severity of fever attacks and should be considered to limit or prevent steroid side effects [21]. With frequent attacks and/or subclinical inflammation between attacks, maintenance therapy with IL-1 blockade [6–8, 22–25] or etanercept [5–7, 26, 27] is recommended and may limit corticosteroid exposure. Canakinumab has been shown to be effective and well tolerated in controlling and preventing flares in patients with MKD in a randomized trial (canakinumab versus placebo) [24]: 57% of the 72 patients with MKD enrolled in the trial had a complete response [defined as resolution of the baseline flare at day 15 (Physician Global Assessment (PGA)) score of <2 plus CRP level of ≤10 mg/L or a reduction by ≥70% from baseline] and no new flare (PGA score of ≥2 and CRP level of ≥30 mg/L) until week 16. If one IL-1 blocking agent at adequate dose is ineffective or intolerable, a switch to another IL-1 blocking agent or another biological agent (including TNF-α blockade or IL-6 blockade) should be considered [18]. Likewise, if TNF-α blockade is ineffective or intolerable, a switch to another biological agent (including an IL-1 or IL-6 blocking agent) should be considered. In selected cases with severe refractory disease with poor quality of life, referral to a specialist center for consideration of allogeneic hematopoietic stem cell transplantation is recommended [28, 29]. Colchicine or statins are not efficacious.

Anti-IL1 blockade may be effective for treating some chronic MKD-associated manifestations, such as erosive polyarthritis [14] and inflammatory bowel disease [10]. Finally, the possibility of macrophage activation syndrome and of severe infections, requiring urgent treatments, should be kept in mind by physicians.

Monitoring in all patients with MKD should include general physical examination with growth and development charts, complete blood count, and inflammatory parameters, such as CRP and serum amyloid protein (SAA), urinalysis for proteinuria and hematuria, ophthalmological examination, and a tool impact of disease on well-being, functioning, and social participation [18].

12.5 Outcome

The incidence of AA amyloidosis is lower than that of other autoinflammatory syndromes. However, it may develop in a few patients [8, 30] and must be regularly searched for. In the Eurofever registry, AA amyloidosis was diagnosed in five out of 114 patients with a median disease duration before the diagnosis of amyloidosis of 23 years (range 8–37 years) [7].

In a subset of patients, the frequency of recurrent febrile attacks gradually decreases with time [6–8, 31]. However, disease activity remained high in other

patients either because of frequent febrile attacks or because of persistent organ involvement, such as polyarthritis and inflammatory bowel disease. In the French series, no significant difference was found between the group with persistently high disease activity or death as compared to the group whose disease activity decreased over time, regarding mean age at disease onset (8.2 months versus 12.2 months), and percentages of patients carrying the p.Val377Ile mutation. MKD-related death has been reported in three patients at the age of 2–3 years—two patients died of multiple organ failure and one patient died of staphylococcal sepsis associated with macrophage activation syndrome [31].

In conclusion, MKD has a broad spectrum of manifestations. It is not only an autoinflammatory syndrome but also a multisystemic inflammatory disorder and a possible immunodeficiency.

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Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS)

13

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13.1 Introduction

Tumor necrosis factor receptor periodic fever syndrome (TRAPS) is an autosomal dominant autoinflammatory syndrome. It is rare with an estimated prevalence of 1–2 per million and an estimated incidence of 1/1,785,000 in children aged 16 years in Germany [1, 2]. It was first described in 1982 as familial Hibernian fever, as the first reported cases were predominantly of Irish ancestry [3]. Since then, it has been reported in multiple ethnic groups, although the reported cases remain largely Caucasian. The name TRAPS was coined with the discovery that mutations in the *tumor necrosis factor receptor superfamily 1A* (*TNFRSF1A*) gene, encoding the TNF receptor 1 are causative [4]. Nonfamilial cases have been reported [5], and genetic studies of families of affected individuals have detected asymptomatic carriers, suggesting variable penetrance [6].

Both sexes are affected with a reported male-to-female ratio of 3:2 [7]. The age of disease onset ranges widely from the neonatal period to adults over the sixth decade of age [8]. The median age of disease onset is 3 years [9], while onset in adult life is reported in about 20% in some studies [8, 10]. Lachmann et al., in a large series of 158 cases, reported a median age of diagnosis of 25.9 years with a median delay in diagnosis of 10.3 years, reflecting the diversity of clinical symptoms and diagnostic challenges [9].

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13.2 Genetics

TRAPS is caused by a mutation in the *tumor necrosis factor receptor superfamily 1A* (*TNFRSF1A*) gene (OMIM*191190) located on chromosome 12. It encodes for the TNF receptor 1 (=55 kDa TNF receptor) and was identified in 1999 [4]. The disease is inherited in an autosomal dominant mode, although the variable penetrance and de novo mutations often complicate the pattern of inheritance. More than 140 different disease-causing mutations have been found in TRAPS (http://fmf.igh.cnrs.fr/infever). Approximately 40% of mutations are specific to an individual or family with TRAPS, and with advances in genetic testing techniques, new variants are constantly found. A recent consensus paper looked at 147 reported gene variants in TNFRSF1A and concluded that only 29% were clearly disease causing, 1% were benign, and the others were much more challenging to interpret [11]. Two low penetrance mutations, c.362G>A (R92Q) and c.224C>T (P46L), can be associated with symptoms, usually with a milder phenotype and low risk of developing amyloidosis. Interpretation of the significance of these variants needs to be done in clinical context, as they are extremely common and observed in 2% and 10% of Caucasians and Africans, respectively, and the vast majority carriers are healthy [12]. Most of the known pathogenic mutations are single-nucleotide missense mutations occurring within exons 2–4 [9] and 6; deletions and deletion/insertion variants have also been reported in the extracellular domain [13]. Mutations resulting in the substitution of a cysteine in TNFR1, which accounts for approximately 50% of reported mutations, have been suggested to be associated with more severe clinical symptoms and increased risk of AA amyloidosis [5]. Other genetic variants affect proline residues (P46L, L67P, S86P, and R92P) or hydrogen bonding within the receptor (T50M, I170N) [14]. Recently, two cases of TNFRSF1A mosaicism have been described [15, 16]. Interestingly, when patients with high-penetrance mutations were compared with patients with low-penetrance mutations, a delay in disease onset along with the absence of the commonest TRAPS manifestations was observed [17].

13.3 Pathogenesis

TNF-α binds to both TNF receptors I and II and is a key player in TNF mediated diseases [18]. TNFRI is expressed in most cell types while TNFRII is typically found on immune and endothelial cells [19]. When TRAPS was first described, reduced cleavage of the extracellular domain of the TNF receptor was found leading to decreased concentration of soluble TNF receptor in serum [4]. However, it is now known that this occurs in only some of the TRAPS mutations and thus cannot fully explain the disease pathogenesis. More recent theories focus on aberrant folding of the extracellular domain of the mutant TNF receptor 1 leading to retention within the endoplasmic reticulum [20] causing intracellular stress, overproduction of reactive oxygen species, and hyper-responsiveness to LPS [21]. Enhanced generation of mitochondrial reactive oxygen species might then stimulate the inflammatory cascade by activating the NLRP3 inflammasome and generating IL-1 [22]. Gene

expression studies suggest that active diseases is associated with increased expression of TNFRSF1A itself, MAPK14, NFKB1, MMP9, and IL-1 beta, as well as genes involved in the TLR signaling pathway. Effective treatment with canakinumab resulted in a dramatic change toward expression patterns seen in healthy controls and induction of neutrophil apoptosis [2]. Despite the recent advances in understanding the pathogenesis of TRAPS, diseases associated with common polymorphisms and mutation negative cases with symptoms highly suggestive of TRAPS highlight that other as-yet known mechanisms may be involved into disease pathogenesis and need to be further elucidated [23].

13.4 Clinical Manifestations

TRAPS is characterized by a wide and heterogeneous range of clinical manifestations. Age of disease onset, attack severity and duration, and accompanied symptoms differ substantially between patients. There is little evidence of robust genotype–phenotype correlation, perhaps reflecting the broad range of identified mutations and their penetrance. The largest published series found no difference in clinical manifestations between patients with childhood or adulthood disease onset and little difference between disease in the pediatric and adult age groups, with only cervical lymphadenopathy, abdominal pain, and periorbital edema more commonly reported in children and chest pain in adults [9].

13.4.1 Systemic Symptoms

In contrast to the other hereditary autoinflammatory syndromes, TRAPS is characterized by long episodes (usually >1 week) of fever accompanied by fatigue, irritability, anorexia, weight loss, and poor growth [9]. The attack duration ranges from few days to over a month with a reported average length of 10 days [9]. Fever attacks tend to recur after minor triggers (i.e., physical trauma and physical and emotional stress) or spontaneously [7]. The frequency of attacks ranged from every few weeks up to 10 years between episodes, although some patients are suffering from continuous symptoms with varying intensity. Fever is commonly present in pediatric cases, while there are adult cases reported without febrile episodes [24].

13.4.2 Cutaneous Manifestations

TRAPS skin manifestations are numerous and varied. The most typical presentation is that of a centrifugal erythematous migratory rash accompanied by significant myalgia underlying the affected area. It often starts as painful, warm macules and papules, progressively forming large patches [7, 25]. Other reported skin lesions include erysipelas-like erythema, edematous plaques, and urticaria type of rash [26]. Skin biopsies of TRAPS cases have demonstrated monocytic and lymphocytic

perivascular infiltrate [26], while cases of small vessel vasculitis have also been reported [27].

13.4.3 Musculoskeletal Manifestations

Myalgia is a very common feature of TRAPS, with some reports suggesting its presence in up to 100% of the reported cases [7]. It usually migrates peripherally in conjunction with the skin lesions and is considered to be due to fasciitis, while underlying muscles are not usually affected [28]. During the migration course, joints can be involved with limitation of the joint movement. Arthralgia is one of the major characteristics of TRAPS attacks present in about 75% of the cases. Arthritis is less commonly observed [25, 29] and nonerosive with large joints more commonly affected. Fasciitis is a rare but dramatic manifestation of attacks [30].

13.4.4 Ocular Manifestations

Ocular manifestations are frequent and vary within cases. Conjunctivitis and periorbital edema are frequently seen, while, in contrast with other autoinflammatory syndromes, intraocular inflammation has not been reported [31].

13.4.5 Gastrointestinal Manifestations

Abdominal pain is one of the main characteristics of TRAPS attacks. It may be the result of sterile peritonitis or can reflect inflammation of the abdominal wall muscles [7]. It can be associated with anorexia, nausea, vomiting, constipation, or diarrhea. Owing to the severity of abdominal symptoms, there is an increased rate of acute abdomen misdiagnosis and unnecessary laparotomy/appendectomy [7]. Oral ulceration is reported in approximately 10% of the affected cases [29].

13.4.6 Cardiorespiratory Involvement

Recurrent pericarditis is a common feature of TRAPS reported in about 25% cases in a European cohort of TRAPS patients [9], but it rarely occurs alone [32, 33]. TRAPS should thus be added to the list of potential causes of recurrent pericarditis of undetermined origin [34]. Cantarini et al. [35] reported a 6% presence of *TNFRSF1A* gene mutations in patients with recurrent pericarditis and suggested that a positive family history of periodic fever syndrome, recurrences of pericarditis episodes, poor colchicine response, and the need for immunosuppressive treatment are clues to prompt a search for *TNFRSF1A* gene mutations [35]. Myocarditis can be another presenting symptom [36]. TRAPS patients are thought to be at increased risk of cardiovascular events (i.e., early-onset atherosclerosis, thrombosis, and

myocardial infarction) [37] that could be the result of chronic inflammatory process [38]. Further studies are needed to assess the actual risk of cardiovascular complications. Chest pain and difficulty in breathing can be related to musculoskeletal involvement or can be the result of pleurisy. It is reported in 17–53% in different cohorts [7, 9].

13.4.7 Other Manifestations

A broad spectrum of clinical manifestations have been reported in TRAPS patients in a variety of cohorts. Lymphadenopathy, hepatomegaly, and splenomegaly [7, 29] are observed infrequently. Testicular pain and scrotal swelling due to inflammation of the tunica vaginalis testis can mimic testicular torsion and epididymitis [7, 34, 39]. Headache and seizures have also been reported [9]. Hemophagocytic lymphohistiocytosis (HLH) is a very rare disease manifestation and can be the presenting feature [40].

13.5 AA Amyloidosis

Ten to 15% of TRAPS patients are at risk of developing AA amyloidosis [7, 29, 41]. Kidneys are most commonly involved with progressive proteinuric renal dysfunction, but the liver and spleen, and gastrointestinal tract can also be affected. The period between disease onset and development of amyloidosis is variable and averages 20 years. The signs and symptoms of amyloidosis include proteinuric renal dysfunction, hepatomegaly, deranged liver enzymes, diarrhea and weight loss, thyroidomegaly, and, eventually, cardiac failure. Patients with mutations affecting cysteine residues are at higher risk of AA amyloidosis [5, 7] but environmental and other genetic factors also contribute to the increased risk [6].

13.6 Diagnosis

After exclusion of infectious and neoplastic causes of recurrent fever, the possibility of an autoinflammatory syndrome should be investigated. The diagnosis of TRAPS should be considered in the presence of recurrent fever and one or more of the above-mentioned clinical manifestations. Key symptoms include the long duration of attacks and the presence of myalgia, rash, and ocular involvement. A positive family history further supports the diagnosis, although it must be recognized that family members can be completely symptomatic. Careful evaluation of clinical manifestations and genetic testing for mutations in the *TNFRSF1A* gene can establish the diagnosis. In 2015, a validated evidence-based tool either for indication for molecular analysis or for clinical classification of patients with suspected autoinflammatory periodic fevers was proposed by the Paediatric Rheumatology International Trials Organisation (PRINTO) [42]. Based on these criteria, the presence of periorbital edema, duration of episodes >6 days, migratory rash (centrifugal

migratory, erythematous patches most typically overlying a local area of myalgia, usually on the limbs or trunk), myalgia, family history and the absence of vomiting, and aphthous stomatitis were classified as TRAPS with 59% sensitivity and 84% specificity [42]. There is still a lot of debate on how to interpret patients in whom the R92Q and P46L variants have been detected in the genetic testing.

13.7 Laboratory Findings

During an acute episode, the following blood tests abnormalities are usually observed: increased neutrophil count, significant increase in acute phase reactants including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum A amyloid (SAA), fibrinogen, ferritin, and serum complement components. A nonspecific polyclonal increase in immunoglobulins (especially IgA) can also be observed. Microcytic anemia of chronic disease can also be present. Reduced soluble TNF receptor levels are seen in many but not all patients. Acute phase reactants may continue to be elevated even between attacks, demonstrating subclinical inflammation. Monitoring of SAA levels throughout the disease course is of high utility, as elevated levels are associated with an increased risk of AA amyloidosis. Moreover, SAA levels can serve as a very good biomarker to monitor disease activity and response to treatment. Finally, frequent monitoring with urine analysis for proteinuria in combination with assessment of the renal function is crucial for early detection of renal amyloidosis.

13.8 Treatment

To date, treatment approaches of TRAPS cases have been mainly based on retrospective cohorts, as only a few placebo-controlled studies exist to guide that decision [43]. In an attempt to standardize treatment strategies, consensus-based recommendations for the management of TRAPS were published in 2015 by a European initiative called Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) [44]. Management of TRAPS cases remains challenging due to the heterogeneity of the genotype and phenotype. The main aim of the therapeutic management is to control the clinical symptoms, improve quality of life, and prevent long-term complications.

Some patients have symptomatic relief with the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Data from an International registry for autoinflammatory diseases (EUROFEVER) published in 2013 where 113 TRAPS patients were included suggested that NSAIDs were prescribed in 48 patients with mainly partial response [43]. Corticosteroids are more effective in treating TRAPS attacks, but unacceptably high doses may be required when attacks are too frequent or there is evidence of continuous subclinical inflammation. Moreover, the effect tends to wean over time [45]. Colchicine has been used to control symptoms with overall

disappointing results [34, 46]. In contrast to those reports, TRAPS cases included in the EUROFEVER registry were prescribed colchicine with a beneficial effect in 21 of 39 patients [43].

Etanercept, a TNF-α blockade agent, has been used with modest success, although the therapeutic effect seems to decline over time [43, 47–49]. In contrast, infliximab, a chimeric human-murine IgG1 monoclonal antibody, and adalimumab, a recombinant IgG1 human monoclonal antibody, seem to be ineffective, and paradoxical inflammatory reactions have been observed [46, 49–51].

IL-1 blocking agents are the current treatment of choice in patients requiring biologics [43] either given on demand or given continuously to control the symptoms [52]. An open-labeled study with canakinumab, a monoclonal antibody directed against IL-1-beta, in which 20 TRAPS patients were included, demonstrated a 95% efficacy in achieving a complete or almost complete response at day 15 [2]. The median time of clinical remission was 4 days [2]. A placebo-controlled study that used canakinumab in TRAPS, mevalonate kinase deficiency, and colchicine-resistant familial Mediterranean fever confirmed the findings [53], leading to US Food and Drug Administration (FDA) and the European Medicine Agency approval of the drug for the treatment of TRAPS in 2017. A potentially alternative to canakinumab is anakinra, the recombinant IL-1 receptor antagonist. Anakinra has been demonstrated to be effective in controlling TRAPS symptoms [52], while its short half-life offers the possibility to be used on demand only during TRAPS attacks [54].

Finally, tocilizumab, a humanized monoclonal antibody to IL-6 receptor, may have a role in anti-IL1-resistant cases. Levels of IL-6 are elevated in patients with TRAPS; thus, suppressing IL-6 levels may help to control the inflammatory attacks. Several case reports support the efficacy of tocilizumab in TRAPS patients who have failed other biologic treatments [55–57].

13.9 Conclusion

TRAPS is a rare, autosomal dominant autoinflammatory syndrome caused by mutations in the *TNFRSF1A* gene. Penetrance is variable. Distinctive features include prolonged fever, myalgias, ocular involvement, and centrifugal migratory rash. Elevated inflammatory markers are noted during and between episodes. Persistent disease activity may result in secondary amyloidosis. Once other causes of prolonged fever have been excluded, the diagnosis of TRAPS may be suspected on the basis of clinical symptoms, increased inflammatory markers, and positive family history. Genetic testing is necessary for confirmation of TRAPS diagnosis. NSAIDs and corticosteroids are the first-line treatment with variable outcomes. The major revolution in managing TRAPS has been the advent of biological therapies, developed to block specific targets of the inflammatory response. Long-term IL-1 blockade appears highly effective in controlling both acute disease manifestations and preventing long-term complications in patients with severe disease.

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Type I Interferonopathies

14

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14.1 Introduction

Among causes of recurrent fevers, a new chapter of autoinflammatory diseases has emerged, the so-called "interferonopathies."

14.1.1 History

Isaacs and Lindenmann described in 1957 a soluble factor capable of interfering with viral agents and called it "interferon" (IFN) [1]. Interferons are part of the first antiviral defense and display key regulatory function in innate and adaptive immune response. Type I IFN represents the largest family of IFNs, comprising IFN-α, which comprises 13 subsets in humans, and IFN-β. IFN can be produced by all nucleated cells in response to viral infection thanks to innate immune sensors (also called *pattern recognition receptors*), which recognize nucleic acids from conserved regions of the viral genome. This first line of protection allows infected cells to produce IFN in response to the presence of exogen nucleic acids in excess.

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Type I interferonopathies refer to a group of diseases encompassing Mendelian and complex diseases associated with an upregulation of type I interferon. Systemic lupus erythematosus was the first noninfectious disease associated with high levels of type I interferon in the serum. Later, Jean Aicardi and Françoise Goutières described a progressive neonatal encephalopathy with genetic transmission mimicking a neonatal infection [2], wherein high levels of type I interferon were found in the serum and cerebrospinal fluid [3]. Since then, numerous monogenic diseases with inflammatory phenotypes and uncontrolled activation of interferon signaling have been described. Considering that type I interferon plays a primary pathogenic role in these disorders, Crow and colleagues proposed to name them "Type I interferonopathies" [4].

14.1.2 Innate Immune Response Sensors

Several distinct receptors can detect nucleic acids and lead to the activation of IFN signaling pathways.

Endosomal Toll-like receptors (TLR)-7 and 9 for B lymphocytes and plasmacytoid dendritic cells and TLR3 and TLR8 for myeloid dendritic cells are involved in extracellular virus detection. Indeed, TLR3 detects double-stranded DNA, and TLR 7 and 8 can recognize single-stranded DNA stemming from viral RNA and non-methylated cytosine-guanine (CpG) islets, and TLR 9 can recognize RNA–DNA hybrids [5, 6].

Nucleic acids can also be detected in the cytoplasm by RIG-I-like receptors (RLR) and intracellular DNA sensors. The RLR family includes RIG-I and MDA5 encoded by *DDX58* and *IFIH1* genes. RIG-I and MDA5 are activated by an intracytoplasmic RNA pattern and lead to type I interferon production [7, 8].

Finally, cytoplasmic DNA sensors can also induce interferon production (cGAS, cyclic-GMP-AMP synthase) [9]. In this pathway, the transmembrane protein from the endoplasmic reticulum STING activates IRF3 and NF-κb leading to proinflammatory cytokines and type I interferon production. This pathway is downregulated by TREX1 exonuclease. Other cytoplasmic DNA sensors exist as DAI (dependent activator of IRF), DNA-PK, and IFI16.

The detection of nucleic acids through these different pathways leads to type I interferon production in response to the activation of regulation factors IRF (IFN regulatory factors).

Type I interferon then links up to the heterodimeric receptor (IFNAR 1 and IFNAR 2) and activates the JAK-STAT signaling pathway, leading to the induction of hundreds of ISG (interferon-stimulated genes) [4, 10].

Interferon production is regularly triggered by the detection of exogenous nucleic acids from viruses, but in some pathological cases, the production is triggered by endogenous nucleic acids derived from endogenous retrovirus sequences present in our genome (HERV). Regulatory mechanisms normally prevent the accumulation of nucleic acids by the presence of exonucleases in the cytoplasm or by keeping innate immune receptors in the endosome, but mutations of these proteins can be responsible of an excessive type I interferon production.

14.2 Pathogenesis of Type I Interferonopathies

Type I interferonopathies are due to aberrant stimulation or unregulated control of the type I interferon system. The excessive production of interferon can appear through three different pathways:

- Nuclease defect (*TREX1*, *SAMHD1*, *ADAR1*, *RNASEH2*, *RNASEH2B*, and *RNASEH2C*) leading to the accumulation of endogenous nucleic acids
- Constitutive activation or enhanced sensitivity of an innate immune sensor, for example, MDA5 (*IFIH* and *DDX58* mutations) and RIG-I, or adaptive molecules (*TMEM173* encoding for STING)
- Defective feedback of the interferon pathway (ISG15 mutations).

14.3 Clinical Features of Interferonopathies

Type I interferonopathies-associated features are very heterogeneous and comprise overlapping phenotypes. Here we expose the typical features and some specificity associated to the causal gene (Table 14.1).

Table 14.1 Type I interferonopathies

Gene name (protein name)	Inheritance	Phenotype	Protein function
TREX1	AR or AD	AGS, FCL, SLE, RVCL	3′–5′ exonuclease
RNASEH2A	AR	AGS	Catalytic component of the RNase H2 complex
RNASEH2B	AR	AGS and spastic paraparesis	Noncatalytic component of the RNase H2 complex
RNASEH2C	AR	AGS	Noncatalytic component of the RNase H2 complex
SAMHD1	AR	AGS, FCL, CLL	dNTP triphosphohydrolase triphosphatase and ribonuclease activity
ADAR	AR or AD	AGS, DSH, BSN, and spastic paraparesis	Hydrolytic deamination of adenosine to inosine in dsRNA
IFIH1 (MDA5) from Crow and Manel, Aicardi-Goutières syndrome, and type I interferonopathies, 2015	AD	AGS, spastic paraparesis, SMS	Cytosolic sensor of dsRNA

(continued)

Table 14.1 (continued)

Gene name (protein name)	Inheritance	Phenotype	Protein function
DDX58 (RIGI)	AD	Atypical SMS	A 5′-triphosphate and 5′-diphosphate dsRNA cytosolic sensor
TMEM173 (STING)	AD	SAVI	An adaptor molecule involved in transducing cytosolic DNA-induced signaling to IFN production
ISG15	AR	Susceptibility to mycobacterial diseases and intracranial calcifications	A negative regulator of type I IFN production by stabilization of USP18
PSMB8	AR	JMP, NNS, JASL, or CANDLE	Part of a multisubunit protease complex responsible for regulating proteolysis in eukaryotic cells
ACP5 (TRAP)	AR	SPCEND, autoimmune phenotypes (SLE)	Lysosomal acid phosphatase activity
SKIV2L	AR	Trichohepatoenteric syndrome	RNA helicase
POLA1	X-linked recessive	XLRPD	Catalytic subunit of the DNA polymerase-α
DNASE2	AR	Pancytopenia, liver fibrosis, membranoproliferative glomerulonephritis, recurrent fevers, anti-dsDNA antibodies	Endonuclease activity

Adapted from Crow and Manel, Aicardi-Goutières syndrome and type I interferonopathies, 2015 [11]
AD autosomal dominant, *AGS* Aicardi-Goutières syndrome, *AR* autosomal recessive, *BSN* bilateral striata necrosis, *CANDLE* chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature, *CLL* chronic lymphocytic leukemia, *DSH* dyschromatosis symmetrica hereditaria, *FCL* familial chilblain lupus, *IFN* interferon, *JASL* Japanese autoinflammatory syndrome with lipodystrophy, *JMP* joint contractures, muscle atrophy, microcytic anemia, panniculitis, and lipodystrophy, *NNS* Nakajo-Nishimura syndrome, *RVCL* retinal vasculopathy with cerebral leukodystrophy, *SAVI* STING-associated vasculopathy with onset in infancy, *SLE* systemic lupus erythematosus, *SMS* Singleton-Merten syndrome, *SPENCD* spondylochondromatosis, *XLRPD* X-linked reticulate pigmentary disorder

14.3.1 Central Nervous System Involvement

Aicardi-Goutières syndrome (AGS) is a neonatal leukoencephalopathy mimicking an infectious neonatal disease (pseudo-TORCH). Patients present an early-onset encephalopathy accompanied to some extent by cerebral atrophy, leukodystophy, and calcifications. Cerebral spinal fluid analysis usually finds lymphocytosis, and all the infectious explorations remain negative, while IFN activity can be increased

[3]. The clinical course evolves into severe neurological involvement with microcephaly, spasticity, psychomotor delay, and early death. Patients can also present other involvements such as chilblain or sometimes glaucoma, hypothyroidism, and cardiomyopathy. AGS is an autosomal disorder. Eight mutations have been reported in this syndrome, and all genes are implicated in nucleic acid metabolism. Most of these mutations are of loss-of-function type, but few are gain-of-function mutations. The mutation of the ubiquitous endonuclease TREX1 results in the accumulation of nucleic acids and in the activation of the STING-dependent interferon pathway [12]. The mutation of RNASEH2 subunits (RNASEH2A, RNASEH2B, and RNASEH2C) leads to a defect in RNA degradation [13]. *ADAR1* and *IFH1* encode proteins implicated in RNA metabolism: ADAR (adenosine deaminase acting on RNA) is involved in RNA editing, and its mutation leads to RNA accumulation and activation of RLR. *IFIH1* encodes MDA5 whose mutations lead to decreased threshold activation in response to double-stranded RNA [14].

SAMHD1 mutations are responsible for a cerebrovascular disease with large vessels aneurysms and early-onset strokes, glaucoma, panniculitis, and nonerosive arthritis. *SAMHD1* mutations are also reported on mild forms of AGS and in familial chilblain lupus without neurological involvement.

Very recently, another mutation has been described in *ISG15*, with patients presenting cerebral calcifications and susceptibility to mycobacterial infections. ISG15 stabilizes the USP18 protein, which is implicated in the negative feedback of interferon signaling [15].

14.3.2 Pulmonary Involvement

Gain-of-function mutations in the *TMEM173* gene encoding the STING protein are responsible for SAVI (STING-associated Vasculopathy with onset in Infancy) with autosomal dominant inheritance. This disease is characterized by early-onset systemic inflammation, severe skin vasculitis leading to extensive tissue loss (chilblain), and severe lung fibrosis [16]. There is a phenotype overlap regarding the vasculitis lesions between SAVI and AGS, but some clinical features are distinct: pulmonary involvement is seen only in SAVI, and SAVI patients do not show neurological symptoms. Importantly, lung disease can be inaugural without additional systemic symptoms [17].

14.3.3 Bone and Vascular Involvement

Mutations in *ACP5* encoding Tartrate-resistant acid phosphatase type 5 (TRAP) are transmitted in an autosomal recessive mode and are responsible for spondyloenchondrodysplasia (SPENCD) with skeletal dysplasia, growth retardation, neurological involvement, and systemic autoimmunity. This latter condition represents an increased susceptibility for Sjögren's syndrome, systemic lupus erythematosus, hemolytic anemia, thrombocytopenia, hypothyroidism, inflammatory myositis,

Raynaud's syndrome, and vitiligo [18]. TRAP is expressed in osteoclasts, macrophages, and dendritic cells, thus explaining both skeletal and autoimmune involvements in SPENCD patients.

Singleton-Merten syndrome (SMS) is an autosomal dominant disorder characterized by aortic and valvular calcifications, dental abnormalities, osteopenia, acro-osteolysis, psoriasis, and glaucoma. Several *IFIH1* mutations and mutations in *DDX58* encoding RIG-I have been reported in this syndrome. The interferon signature is positive in these patients classifying SMS among the interferonopathies [19].

14.3.4 Skin Lesions

Chilblain-like skin lesions can be observed in familial chilblain lupus related to mutations in *TREX1*, *SAMHD1,* and *TMEM173*. They are seen in AGS, SPENCD, and SAVI. These chilblain are evocative for type I interferonopathies (Fig. 14.1). Concerning other skin lesions, telangiectasias are reported in SAVI patients, and psoriasis is seen in Singleton-Merten syndrome.

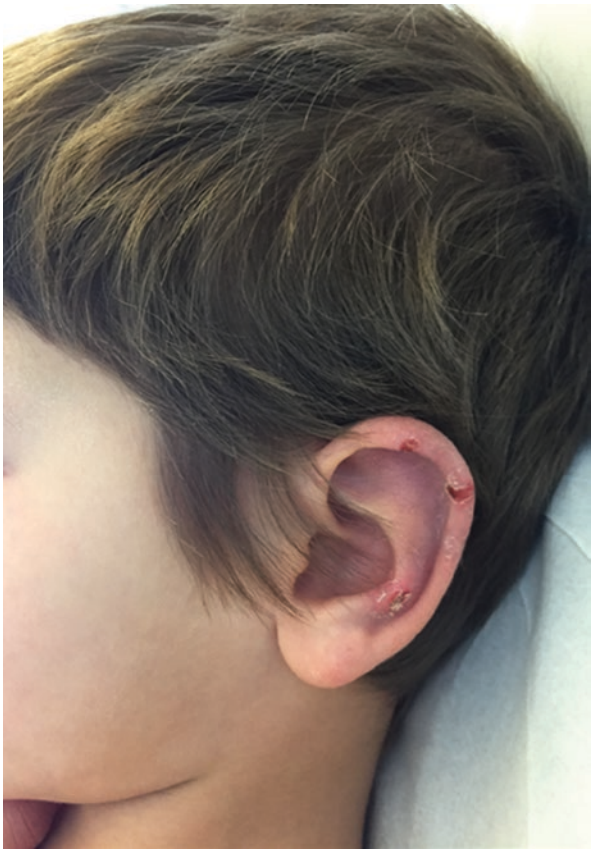

Fig. 14.1 Antihelix chilblain in a patient with AGS (TREX1 mutation)

14.3.5 Autoimmunity

Type I interferonopathies can be associated with autoimmunity, in particular with systemic lupus erythematosus (SLE). SLE was the first disease described with high interferon levels, and more than 90% of juvenile SLE patients have a positive interferon signature [20]. SLE is a multifactorial disease involving hormonal, environmental, and genetic factors. Juvenile SLE seems to rely more on genetic factors since a Mendelian transmission has been observed in some families. Some monogenic forms of lupus were associated with mutations causing AGS as *TREX1*, *SAMHD1*, *ACP5,* and *RNASEH2*.

DNase II deficiency due to biallelic loss-of-function mutations has been described recently. DNase II digests DNA of apoptotic cells from nuclei extruded from erythroid precursors, so DNase II deficiency leads to the accumulation of DNA in the lysosomes and to the production of type I interferon. Patients present severe neonatal anemia with membranous glomerulonephritis, liver fibrosis, deforming arthropathy, and anti-DNA antibodies [21].

14.3.6 Gastrointestinal Involvement

Tricho-hepato-enteric syndrome is caused by *SKIV2L* mutation and is responsible for severe diarrhea and liver dysfunction [22, 23]. Loss-of-function mutations of this RNA helicase lead to an aberrant activation of the RLRs. It is interesting to notice that patients can present the same phenotype with a different genetic background and a negative interferon signature, suggesting that the symptoms are not related to type I interferon production.

14.3.7 Other Type I Interferonopathies

Proteasome-associated autoinflammatory syndrome (PRAAS) is an autoinflammatory disease consisting in recurrent fever, panniculitis, and lipodystrophy and has been found with positive interferon signature. *PSMB8* encodes a proteasome subunit, and its mutation leads to proteasome dysfunction, accumulation of ubiquitinylated proteins, and autoinflammation [24].

The X-linked reticulate pigmentary disorder (XLRPD) is a genodermatosis with autoinflammatory features linked to the intronic mutation of *POLA1,* which encodes a catalytic subunit of the DNA polymerase-α.

14.4 Laboratory Tests

No test assessing type I interferon status is currently available in routine medical practice. Indeed, type I interferon level is very low and difficult to measure in the serum of patients. Therefore, it is not a reliable biomarker since it falls with age after an early peak during the acute phase in children affected by AGS.

However, Rice et al. showed that the type I interferon upregulation was correlated with the increased expression of a subset of six genes "interferon signature genes" (IFI27, IFI44L, IFIT1, ISG15, RSAD2, and SIGLEC1) in AGS patients, the so-called "interferon signature" [25]. Interferon signature can be used both for the diagnosis of type I interferonopathies and to follow disease activity.

Recently, a new interferon score has been published using Nanostring technology. Kim et al. developed a 28 interferon-response-gene (IRG) scoring system to quantify the expression of putative IRGs selected in a patient with the IFN-mediated disease chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) and another patient receiving pegylated-IFNα2 for chronic hepatitis C [26]. The score was validated in SAVI patients as positive controls and neonatal-onset multisystem inflammatory disease (NOMID) patients and in healthy donors for negative controls [26].

This score allows the diagnosis of type I interferonopathy, but genetic analysis is required for precise diagnosis of the mutation. In the case of high clinical suspicion of type I interferonopathy for a patient with negative interferon score, genetic testing remains mandatory.

14.5 Therapeutic Options

Type I interferonopathies are a heterogeneous group of diseases, but they share a common pathogenesis with an excessive type I interferon production. This excess of IFN is supposed to be causal of the main features [27]. Therefore, the blockade of the interferon signaling pathway seems to be logical in this context.

JAK inhibitors are particularly promising because they block the signaling downstream the activation of the IFN receptor. Baricitinib and ruxolitinib are both JAK1/2 inhibitors and have shown interesting preliminary results for their safety and efficacy in SAVI and CANDLE [28, 29], although the IFN score was not abrogated in SAVI patients.

Monoclonal antibodies targeting IFNα (sifalimumab) and IFNAR (anifrolumab) have been tested in SLE and are promising therapeutic options for type I interferonopathies [30]. Finally, as the HERV is supposed to be partially responsible for the increase of intracytoplasmic nucleic acids in AGS with enzymatic defect, it is supposed that reverse transcriptase inhibitors used for patients with human immunodeficiency virus (HIV) may represent an option in the future by targeting the endogenous retroviruses and decreasing IFN signature [31].

14.6 Conclusions

Next-generation sequencing allowed us to define new inherited inflammatory disorders by the discovery of new actors and inflammatory pathways involved in type I IFN homeostasis. Furthermore, the measurement of selected IFN-stimulated genes can strengthen the diagnosis of type-I interferonopathies. Drugs blocking type I IFN

itself, the receptor, or the downstream signaling represent promising strategies to improve patient care and our understanding of the role of IFN in the disease pathogenesis.

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Rare Monogenic Causes of Periodic Fevers

15

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15.1 Haploinsufficiency of A20 (HA20)-AISBL

15.1.1 Introduction: Definition

Haploinsufficiency of A20 (HA20) is an autoinflammatory disorder, which is inherited autosomal dominantly and known as a familial Behçet-like autoinflammatory syndrome (AISBL). This molecular diagnostic term was described in patients who have been diagnosed as either classical Behçet Disease or other common disorders such as JIA, RA, SLE, type 1 diabetes, psoriasis, celiac disease, and coronary arterial disease. There are some similarities and differences between classical Behçet Disease (BD) and this genetic autoinflammatory Behçet-like disease [1]. The disease was first described in 2016 by Zhou et al. in 11 patients from six distinct families [2]. Currently, 45 cases have been described in the literature [1, 2–5].

Haploinsufficiency of A20 is twice as prevalent in females as that in males. The characteristic features of the disease are recurrent fevers; Behçet-like oral and genital ulcers; arthritis; uveitis; gastrointestinal symptoms such as abdominal pain, digestive ulcers, or diarrhea; and skin lesions such as erythema nodosum [1]. One of the differences of this syndrome from classical BD is the onset of the disease reported in childhood instead of mostly adulthood (BD) , with the symptoms starting between 1 and 10 years of age; furthermore, recurrent fever is a more common feature. Detection of the HLA B51 antigen is unusual, and gastrointestinal symptoms are over-represented compared to classical BD [1]. Clinical manifestations and disease course may vary

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even among patients with the same mutation in TNFAIP3 [3]. This suggests a role for modifying alleles in the disease progression and possible contribution of environmental factors. Currently, this newly described disease's clinical manifestations, disease progression, severity of symptoms, and complications are not well characterized in the literature. Because the targeted therapies may alter disease course and improve the outcome, early recognition and diagnosis are critical.

15.1.2 Etiology: Pathogenesis

This is an autosomal dominant inherited autoinflammatory disease considered as a monogenic form of BD due to highly penetrant novel germline mutations in TNFAIP3 and earlier onset symptoms [3]. The disease's first described series, one single mutation in the TNFAIP3 gene, was found as a cause of functional A20 enzymatic pool decline, which is called haploinsufficiency of A20 [1, 2]. The TNFAIP3 protein includes 790 amino acids; it is also known as A20 and encoded by the TNFAIP3 gene located on chromosome 6q23.3, and it plays a critical role in the negative regulation of inflammation and immunity [1, 3]. A20 is an ubiquitin-editing (deubiquitinase; DUB) enzyme that has crucial function in the inhibition of key proinflammatory molecules, including inhibitor of nuclear factor kappa B kinase subunit gamma (IKKγ (NEMO)) and receptor-interacting protein kinase 1 (RIPK1), in the canonical NF-kB and other signaling pathways. The enzyme has dual activities that remove K63-linked ubiquitin chains with N-terminal ovarian tumor domain-mediated deubiquitinase activity from key adaptor proteins, replacing them with K48-linked polyubiquitin chains with C-terminal zinc finger-mediated E3 ubiquitin ligase activity, to mark them for proteasomal degradation and termination of the NF-kB activation cascade [4].

HA20 was described as an autoinflammatory disease caused by heterozygous loss-of-function mutations in TNFAIP3 [2]. These mutations lead to insufficient DUB activity of TNFAP3 (A20) and cause amplified NF-kB signaling and phosphorylation of c-Jun N-terminal kinase and p38 mitogen-activated protein kinases (MAPKs). Mutant A20 cells lose the hydrolyzing function of K63 ubiquitin chains from NEMO/IKK, RIPK1, and TNF Receptor 1 (TNFR1). Production of proinflammatory cytokines including IL-1, IL-6, IL-9, IL-17, TNF, IP-10/CXCL10, and IFNγ increases excessively with the activity of the NF-kB, and MAPK pathways and NLRP3 inflammasome by the accumulation of K63 ubiquitin proteins. In wild-type models, NLRP3 inflammasome activity is downregulated by A20; consequently, in HA20 patients, there is increased NLRP3 activity.

Multiple autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes mellitus, inflammatory bowel disease, Sjogren's syndrome, and psoriasis have been associated with common low-penetrance coding and noncoding variants in the TNFAIP3 gene. Identification of additional HA20-associated mutations is essential to better recognize the full spectrum of phenotypes associated with the distribution of pathogenic mutations in A20 [3]. Also suggested as a tumor suppressor gene, A20's somatic inactivating mutations have been identified in B cell

lymphomas; however, none of the patients developed lymphoma or malignancy in the literature [3, 6]. Duncan et al. reported a case of early-onset autoimmune disease (insulin-dependent diabetes, hepatitis, enteropathy, and interstitial lung disease), and Takagi et al. presented a case with autoimmune lymphoproliferative syndrome-like phenotype, and both cases had germline mutations in the TNFAIP3 gene [7, 8]. In one study, five patients developed autoantibodies; however, only one patient was diagnosed with an overt autoimmune disease [2]. In heterozygous murine models, partial deficiency in the gene causes the existence of auto-antibodies combined with symptoms remarkably similar to human diseases. A complete deficiency in the protein has never been described in humans [1]. The spectrum of reported clinical phenotypes associated with TNFAIP3 gene mutations reminds us of the importance of A20 in immune regulation and autoimmune pathogenesis.

15.1.3 Epidemiology

According to the last published review by Berteau et al. in 2018, there are 45 cases of AISBL in the literature reported since its discovery in 2016. Compared to classical BD, there is a reversal of the sex ratio to 1:2 with 15 men and 30 women, respectively [1]. Distribution of the disease is global with affected probands from Caucasian origin to Middle or Far East.

15.1.4 Clinical Manifestations

The first onset of the clinical manifestations occurs with an interquartile range of 1–10 years and a median age of 5.5 years [1]. Sixty-nine percent of patients meet the criteria of Behçet disease according to ICBD 2016. The most common manifestations were oral (87%) and genital (67%) ulcers, fever episodes (62%), gastrointestinal features (60%), skin involvement (53%), of which 13% was erythema nodosum or pseudo folliculitis (Fig. 15.1) as described by Davatchi [9]. Forty-two percent of patients had musculoskeletal involvement including arthritis (11%). Some patients experienced ophthalmological features different from classical BD. Recurrent upper respiratory tract infections, thyroiditis, neurological manifestations, and vascular features such as CNS vasculitis were rarely noticed (Table 15.1).

15.1.5 Diagnosis

AISBL should be considered in cases of early childhood-onset Behçet-like phenotype and in familial BD patients. Sequencing of the TNFAIP3 gene is required to confirm diagnosis. Unlike BD, HLA B51 antigen and pathergy testing is rarely positive. Laboratory tests demonstrate high acute phase reactants. In the cohort of Berteau et al., 16 patients had autoantibodies such as ANA, lupus anticoagulant, and anti-TPO [1].

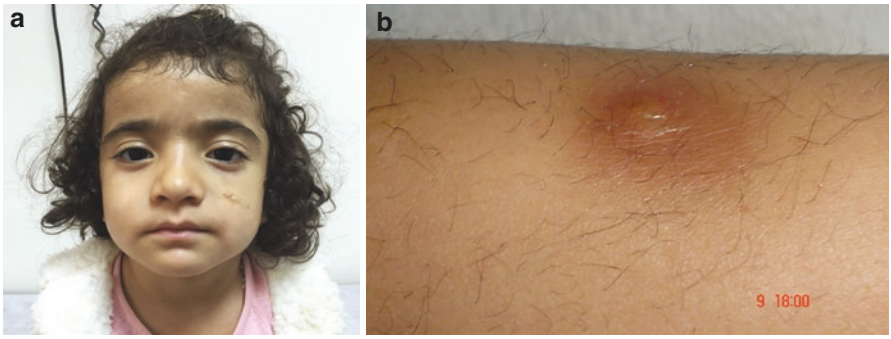

Fig. 15.1 (**a**, **b**) One of the first patients in the literature. Folliculitis is described in patients with AISBL. Hirsutism is one of the numerous potential side effects of excessive corticosteroid treatment, which can be seen in **a** and **b**

Table 15.1 Clinical manifestations in patients with AISBL associated with TNFAIP3 mutations

Clinical manifestation	Range
Oral ulcers	39/45
Genital ulcers	30/45
Recurrent fevers	28/45
Skin features (erythematous papules, erythema nodosum, folliculitis, skin abscesses)	24/45
Gastrointestinal (ulcers, colitis, digestive hemorrhages, hepatitis)	27/45
Musculoskeletal (polyarthritis, arthralgia, myalgia)	19/45
Eye (uveitis, retinal vasculitis)	6/45

Differential diagnosis includes other monogenic autoinflammatory disorders such as mevalonate kinase deficiency (MKD), Blau syndrome/early-onset sarcoidosis, familial Mediterranean fever (FMF), and pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA), which are presenting with combinations of recurrent fevers, orogenital aphthosis, arthritis, skin lesions, and uveitis. It is important to be aware of patients who have destructive gastrointestinal manifestations such as inflammatory bowel disease at an early age, a diagnosis of AISBL should be considered. Prospective evaluation of a larger cohort of AISBL cases is necessary to characterize the full clinical spectrum of this disease [1].

15.1.6 Management

Colchicine has been effective in the control of orogenital ulcers and skin lesions in some patients [4, 5, 7, 10].

Various immunosuppressive treatments have been given to this group of patients. Glucocorticoids have been found to be a potent inhibitor of the NF-kB pathway. Because of the wide systemic inflammation, cytokine inhibitors such as TNF alpha

antagonists (infliximab, adalimumab, etc.), IL-1 blockers (anakinra and canakinumab), anti-IL-6 (tocilizumab), and immunosuppressive agents such as methotrexate and cyclosporine have been used to control the disease activity. No mortality has been reported to date among genetically identified patients in the literature [3, 8, 11]. Clinical progression and response to treatment is unpredictable; therefore, future studies are required to understand treatment response, prognosis, and long-term morbidity and mortality required to optimally manage this rare autoinflammatory disease.

15.2 Otulipenia

15.2.1 Definition

Otulipenia is a systemic autoinflammatory disease caused by a loss-of-function mutation in the OTULIN (FAM105B) gene, encoding a deubiquitinase (DUB) with linear linkage specificity [12]. OTULIN has a part in adapting innate immune signaling complexes. Excessive linear ubiquitination of target proteins such as NEMO, RIPK1, TNFR1, and ASC in OTULIN-deficient patients leads to severe inflammation and clinical symptoms. As discussed in Haploinsufficiency A20 disease, the discovery of DUB activity adds to the growing collection of human diseases caused by defects in the ubiquitin pathway and advocates for the role of targeted cytokine therapies. A novel homozygous mutation in the FAM105B gene was first identified in one Pakistani and two Turkish families with four affected patients described by Zhou et al. in 2016 [12]. Heterozygote carriers were asymptomatic, which suggested that a reduced protein expression of OTULIN is sufficient for immune homeostasis regulation.

15.2.2 Etiology/Pathogenesis

Post-translational protein modification by ubiquitination is essential for many biological regulatory processes such as DNA repair, endocytosis, transcription, protein degradation, and preservation of cellular homeostasis [10, 12]. Linear or methionine 1-linked ubiquitination is catalyzed by the linear ubiquitin (Ub) assembly complex called LUBAC, which holds HOIL-1, HOIP, and SHARPIN molecules [13]. Currently, LUBAC is the only E3 ubiquitin ligase known to generate linear polyubiquitin chains and plays a crucial role in the activation of NF-kB signaling by ligating linear Ub to its target proteins, which include NEMO (NF-kB essential modulator) and RIPK1(receptor-interacting serine/threonine protein kinase 1) [13, 14].

OTULIN is a 352-residue highly conserved protein that consists of N-terminal LUBAC-binding domain and C-terminal ovarian tumor (OTU) domain with a specific activity to hydrolyze linear (Met1)-linked Ub chains [10, 12]. The OTU domain and binding of OTULIN to linear Ub chains are affected by disease-associated mutations. OTULIN restricts NF-kB signaling activity through direct interaction

with HOIP. Mutant OTULIN proteins cannot restrict the accumulation of Met1 Ub chains on target substrates (IKK/NEMO, RIPK1, and ASC) [10]. Thus, many pro-inflammatory cytokines are overproduced including TNF, IL-1β, IL-6, IL-17, IL-18, and IFN-γ [13].

Otulipenia, also called OTULIN-related autoinflammatory syndrome (ORAS), has been showing to arise from several homozygous loss-of-function mutations [14]. Otulipenia-related mutations result in OTULIN dysfunction rather than a quantitative deficit [15]. At a molecular level, different residual amounts of OTULIN proteins were expressed between cells. Measured cytokine levels correlated with the activity level of the disease [15]. Boisson and colleagues reported three RBCK1 (HOIL-1)-deficient and one RNF31 (HOIP)-deficient patient [16, 17]. Fibroblasts of these four patients showed less linear Ub accumulation and reduced NF-kB signaling, comparative to those of controls, while patients' monocytes were hyperactivated with IL-1β stimulation.

15.2.3 Epidemiology

Otulipenia is a newly identified disease with only four patients described to date; the etiology remains speculative. Three homozygous mutations in the OTULIN/FAM105B gene were identified using a combination of exome sequencing and candidate gene screening in unrelated families of Pakistani and Turkish descent [12]. Unaffected parents and siblings were carriers for the individual mutations, and none of the mutations were reported in public databases or detected in 1630 Turkish healthy controls according to Zhou et al. [12]. Further genetic and clinical studies are required.

15.2.4 Clinical Manifestations

For a better understanding, each disease clinical manifestation will be described for the three patients in the literature. Patient 1, from a large consanguineous family, was born prematurely and soon after birth presented with fever and rash. Two of his first cousins died due to a similar disease in early childhood, one of whom was found to have the same homozygous mutation. Failure to thrive, joint swelling, lipodystrophy, and diarrhea were other findings described in this patient. Patient 2 presented at the age of 4.5 months with prolonged fever and a pustular scarring rash. Skin biopsy revealed panniculitis and a neutrophilic dermatosis. Patient 3 presented with neonatal-onset fever and prominent cutaneous lesions including an erythematous rash with painful skin nodules. Her skin biopsy showed a predominantly septal panniculitis with vasculitis of small- and medium-sized blood vessels. Arthralgia, progressive lipodystrophy (Fig. 15.2), and failure to thrive were other manifestations [12].

Patients did not have clear evidence for a primary immunodeficiency and suffered from immunosuppressive therapy-related infections. Two of the patients had

Fig. 15.2 Facial feature of the patient with otulinemia, which is characterized by prominent fat loss (lipodystrophy)

normal to high levels of T, B, and natural killer cell, and Ig levels were normal to high. T- and B-cell responses were normal. Patients had acceptable specific antibody responses to vaccines or natural infections when tested [12].

15.2.5 Diagnosis

Similar to other rare monogenic autoinflammatory diseases, cardinal clinical features should prompt physicians to consider otulipenia in the context of an early onset of unexplained recurrent fever, recurrent cutaneous rash or arthralgia/arthritis, onset during early childhood, family history of similar disorders, elevated acute phase reactants during episodes and normalization during symptom-free intervals, late complications of continuous systemic inflammation, such as AA amyloidosis, and absence of obvious differential diagnosis [15].

Practitioners should also look for specific signs, which may include but not limited to urticarial-like rash, pustular dermatosis resembling psoriasis or acne, erysipelas-like erythema, aphthosis, recurrent or unexpected pharyngitis/cervical adenitis, conjunctivitis/uveitis, diarrhea/colitis, lipodystrophy/panniculitis or

erythema nodosum-like nodules, and arthritis/arthralgias, which may help differentiate from other autoinflammatory diseases and help further molecular analyses.

15.2.6 Management

Preservation of immune homeostasis is a highly balanced act that requires the coordinated action of many proteins to allow optimal and efficient immune responses. Given the importance of the ubiquitination in cellular physiology, the ubiquitin protein system has produced a substantial interest for drug development [10]. One of the reported cases of otulipenia was partially controlled with a TNF inhibitor (etanercept); however, she is still steroid dependent. Therefore, targeting TNF may be a promising treatment option.

A key challenge for finding effective drugs would be in developing cell-based therapies. The ubiquitination process is regulated at multiple levels of generation, recognition, and removal. Targeting more mechanisms of the Ub-proteasome pathway seems to provide new prospects for therapeutic exploitation and drug discovery [10].

15.3 DIRA (Deficiency of Interleukin 1 Receptor Antagonist)

15.3.1 Definition

DIRA (deficiency of interleukin 1 receptor antagonist) is an autoinflammatory disease characterized by neutrophilic pustular dermatosis, periostitis, aseptic multifocal osteitis, and high acute phase reactants [18, 19]. Interleukin 1 (IL-1) receptor antagonist is the first described endogenous cytokine receptor antagonist, and it normally inhibits the activities of IL-1 [20]. In DIRA, unopposed IL-1 activity is the primary problem. DIRA was described first in 2009 in two articles by Aksentijevich et al. and Reddy et al. [18, 19]. To date, there are around 20 cases reported [19–26]. Almost all the DIRA cases were symptomatic within the newborn period [22, 27].

15.3.2 Etiology: Pathogenesis

DIRA is caused by loss-of-function mutations in the IL1RN gene, which encodes for the IL-1 receptor antagonist [18, 19]. It is autosomal recessively inherited, and carriers are asymptomatic. The mutations in the IL1RN gene result in the absence of production of a functional IL-1 receptor antagonist. Therefore, IL-1 signaling in response to various triggers goes uninhibited in these patients.

15.3.2.1 Epidemiology

Missense and nonsense mutations in the IL1RN gene triggering DIRA have been found in Puerto Rico, the Netherlands, Newfoundland/Canada, Palestine/Lebanon, and Brazil populations. Further studies are required to identify the worldwide epidemiology of this new autoinflammatory disease.

Table 15.2 Clinical features of DIRA

Systems	Major (signs/symptoms)	Minor (signs/symptoms)
General	Fetal distress Prematurity Failure to thrive Growth retardation	Fever
Mucocutaneous	Neutrophilic pustular skin eruption (may heal with scars) Skin abscess Nail dystrophy	Oral mucosal lesions Skin pathergy
Musculoskeletal	Multifocal aseptic osteitis Periostitis Epiphyseal ballooning of long bones/ribs Metaphyseal erosions in the long bones Arthralgia/arthritis	Nonunion of the odontoid Muscle atrophy[a] Osteopenia
Hematological	Anemia Leukocytosis/neutrophilia Venous thrombosis Hemophagocytosis[a]	Thrombocytosis
Gastrointestinal	Ascites (due to portal vein thrombosis)[a]	Gastroesophageal reflux[a]
Cardiovascular	Dilated cardiomyopathy[a]	
Respiratory	Respiratory distress/insufficiency Interstitial fibrosis Atelectasis Pulmonary hemosiderosis[a]	Apnea[a]
Central nervous system	Cerebral vasculitis/vasculopathy[a] Delay in motor development[a]	
Ophthalmological	Episcleritis[a] Corneal lacerations/ulcers[a]	

[a]Present in one patient only

15.3.2.2 Clinical Manifestations

Similar to other hereditary autoinflammatory diseases, DIRA patients exhibit features characteristic of all autoinflammatory disease but also cardinal features that suggest this condition. First clinical manifestations were seen in the neonatal period, including skin pustules, joint swelling, painful osteolytic lesions, and periostitis where the distal ribs, and the long bones were affected particularly. Fever developed rarely and, when present, was often low grade with elevation of acute phase reactants such as erythrocyte sedimentation and C-reactive protein. Pathergy test was positive after mechanical trauma [28]. Other mucocutaneous lesions include neutrophilic pustular skin eruption, skin abscess, nail dystrophy, and oral mucosal lesions in some cases. Other systemic findings are described in Table 15.2.

15.3.3 Diagnosis

Providing optimal medical management for DIRA patients hinges on timely and accurate diagnosis. Prompt recognition of the cardinal clinical manifestations is

crucial. The diagnosis is made by genetic testing for IL1RN mutations [18, 19]. Radiological tests may support the diagnosis, which may include multifocal osteitis in long bones and ribs, heterotopic ossification, and periarticular soft tissue swelling [24]. Biopsies of the affected sites such as skin and bone can be supportive of the diagnosis. In skin biopsies, extensive infiltration of the dermis and epidermis by neutrophils, acanthosis, hyperkeratosis, pustule formation along hair follicles, and perivascular dermatitis can be seen [21]. Purulent osteitis, fibrosis, and sclerosis are seen in the bone biopsy.

Neutrophilic infiltrates in the skin and bone lesions and blood neutrophilia in DIRA patients need to be differentiated from infectious osteomyelitis and congenital/perinatal systemic infections in the newborn period [21]. Furthermore, a lack of response to antibiotics as well as negative bone/blood cultures differentiates DIRA from the etiology of other infections in patients.

DIRA also shares clinical similarities with NOMID (neonatal-onset multisystem inflammatory disease) and Majeed syndromes [25, 27]. Nevertheless, in NOMID, central nervous system involvement is much more obvious with recurrent aseptic meningitis, cochlear inflammation, and mental retardation, and bone lesions are mainly seen in DIRA. Likewise, in DIRA, skin lesions are pustular with urticaria-like neutrophilic lesions seen in NOMID cases. Both Majeed and DIRA patients have chronic recurrent multifocal osteitis and neutrophilic dermatosis, whereas congenital dyserythropoietic anemia is only present in Majeed syndrome [25, 27]. Genetic testing is essential to discriminate these diseases.

15.3.3.1 Management

IL-1 receptor antagonist supplementation is the definitive treatment for DIRA [29]. Anakinra (IL-1 receptor antagonist) causes a rapid clinical improvement in DIRA patients [18]. Few patients may also reply partially to corticosteroid therapy [21]. There is no consensus on the duration of anakinra treatment. Yet, since previous reports of attempts to stop anakinra have led to disease flares, patients may require life-long treatment [23]. There is one case report of effective use of canakinumab (long-acting anti-IL-1 therapy) in DIRA [24].

Five of the reported DIRA patients in the literature have died due to multiorgan failure secondary to severe inflammatory response syndrome ($n = 2$), multiorgan failure and hemophagocytosis ($n = 1$), complications of pulmonary hemosiderosis with progressive interstitial fibrosis ($n = 1$), and intrauterine demise ($n = 1$) [18, 20].

15.4 DITRA (Deficiency of Interleukin-36 Receptor Antagonist)

15.4.1 Definition

The recently discovered IL-36 cytokine family is emerging as significant mediators for inflammatory diseases. The IL-36 subfamily involves three ligands—IL-36α, IL-36β, and IL-36γ—and the natural antagonist IL-36Ra. A rare multisystemic

autoinflammatory disorder characterized by repeated fever episodes with generalized pustular psoriasis (GPP) has been the most convincing association between the IL-36 family and human disease [30]. In 2011, Marrakchi et al. identified IL36RN (the gene that encodes the IL-36 receptor antagonist) as the putative gene for autosomal recessive familial GPP and termed this as the deficiency of the IL-36 receptor antagonist (DITRA) [31]. To date, a comprehensive in vitro functional analysis of all identified IL36RN mutations associated with GPP proved that most mutations cause a complete lack of or substantial reduction in IL-36Ra expression and activity [32].

15.4.2 Etiology: Pathogenesis

The IL-1 family involves 11 molecules, and excessive expression of IL-36 proteins belonging to interleukin-1 subfamily in the skin and disinhibition of the signaling pathway of these proteins' activation lead to an autoinflammatory disease, GPP [31]. Interleukin-36Ra (also known as IL-1F5) is an antagonist of three cytokines, IL-36α (IL-1F6), IL-36β (IL-1F8), and IL-36γ (IL-1F9), which are involved in activating several proinflammatory signaling pathways such as the nuclear factor-kB and mitogen-activated protein kinase pathways (Fig. 15.3). The exact etiology of the disease is still unclear, and there are some studies showing the feasible mechanism underlying the signaling pathway. According to Johnston et al. and Towne et al., IL36RN and its paralogs IL36A, IL36B, and IL36G are abundantly expressed in the skin, and the proteins encoded by these genes modulate NF-kB signaling through their interaction with the IL-1RL2 receptor [33, 34]. Sims and Smith suggested that IL36RN antagonizes the activity of IL-36A and IL-36G by hindering the enrollment of the IL-1RL2 receptor complex [35]. Furthermore, IL36RN itself comprises a putative signal peptide followed by a large IL-1 homology motif, therefore, reflecting the typical domain architecture of IL-1 family cytokines [36].

In 2017, Verena Schmitt et al. discussed that the crosstalk between plasma cells and synovial fibroblasts is mediated by IL-36 receptor. According to this study, IL-36α is expressed in B cells and upregulated in plasma cells. Here, detailed analysis of signaling pathway upon IL-36α stimulation of fibroblast-like synoviocytes, exposed activation of the p38/HSP27 pathway and p38MAPK and NF-kB pathways [37]. Further genetic and immunological studies are necessary to further our understanding of the etiopathogenesis of DITRA.

15.4.3 Epidemiology

DITRA was first described in nine Tunisian families [31]. It has been further characterized by two distinct phenotypes, which are pediatric onset of GPP (PGPP) and adult onset of GPP (AGPP). Li et al. compared the IL-36RN mutations association between PGPP and AGPP in 11 patients of African, European, and Asian origin. In that study, they found that the percentage of IL-36RN mutations of PGPP patients was much higher than that of AGPP patients. They also discussed the possibility of

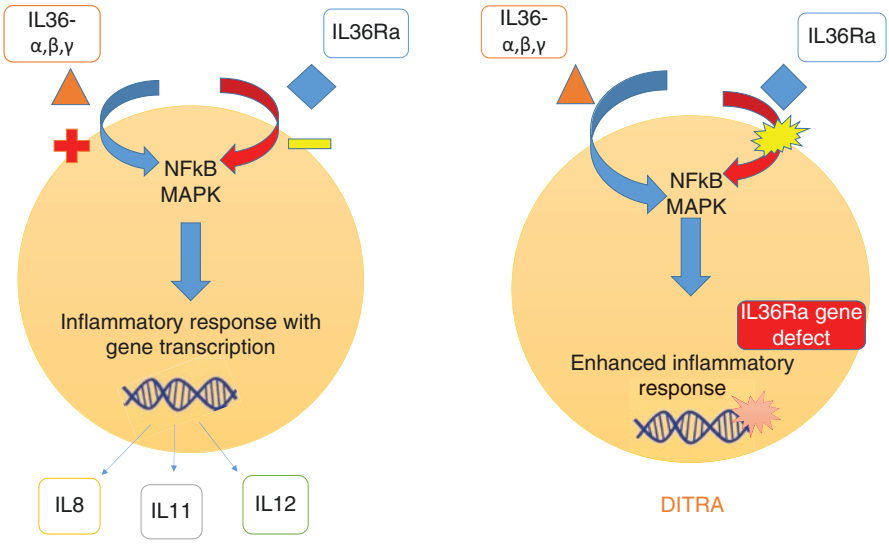

Fig. 15.3 In normal functional cell, IL36Ra regulates IL36-α, β, γ cytokine response with gene regulation. In DITRA, because of the IL36Ra gene defect, IL36Ra cannot lead to NF-kB and MAPK response and the cell reacts with enhanced inflammatory cytokine release

the existence of environmental factors or other regulatory genes may also have a role in the pathogenic process of GPP patients with DITRA [38].

15.4.4 Clinical Manifestations

DITRA is a potentially life-threatening condition if not treated. This autosomal recessive autoinflammatory disease is defined in GPP patients characterized by sudden, repeated episodes of high-grade fever, generalized rash, and disseminated pustules, with hyperleukocytosis and elevated C-reactive protein levels, which may be associated with plaque-type psoriasis [31]. Bonekamp et al. identified two pediatric cases with a severe clinical course [39]. The first patient was a boy who presented at the age of 3 years with inverse psoriasis in the genital area. He later developed diffuse pustular lesions associated with fever and elevation of acute phase reactants, and compound heterozygosity for the IL36RN P76L/S113L mutations has been observed in the patient. The second patient was a 5-year-old girl presenting with erythroderma and pustular lesions, covering more than 85% of her body surface at the age of 1-month-old who also had fever, elevation of acute phase reactants, and failure to thrive. Genetic analysis revealed a homozygous L27P mutation in the IL-36RN gene. After this study, Cherqaoui et al. reported another pediatric case from consanguineous Tunisian parents who had diffuse inflammatory pustular psoriasis and erythrodermic extension at the onset age of 1 month of life [40]. He had fever, irritability, severe failure-to-thrive and recurrent diarrhea, microcephaly, and

a triangular chin at the age of 2 months. Laboratory studies showed markedly increased leukocyte/neutrophil/platelet counts during flares, conversely with normal erythrocyte sedimentation/C-reactive protein rates. Another case whose cutaneous lesions varied from psoriasis vulgaris in infancy to annular pustular psoriasis with acute exacerbation to GPP at 13 years of age was reported in 2017 by Koike et al. [41]. During disease flares, he had mild fever.

15.4.5 Diagnosis

Diagnosis of DITRA includes genetic evaluation of the IL-36RN in GPP patients. The spectrum of mutations for this new disease in many populations is still unclear. Several Japanese patients and one Arab-Palestinian patient have been identified with c.28C>T mutation [42]. Diagnosis of GPP is critical to consider DITRA diagnosis. Because it is a life-threatening condition, urgent genetic testing should be considered in patients with recurring episodes of fever and GPP. Differential diagnosis includes related pustular disorders, palmoplantar pustulosis, acrodermatitis continua of Hallopeau, and acute generalized exanthematous pustulosis, which are also other phenotypes of IL-36RN mutations.

15.4.6 Management

The early age of onset, parental consanguinity, and resilient to therapy provoke to doubt DITRA [42]. Given the lack of clinical response to psoriasis vulgaris treatment such as high-dose corticosteroids and retinoid acid, by the description of the etiology, IL-1 receptor-related drugs used were effective in some patients [43, 44]. In IL-1 receptor antagonist-resistant patients, etanercept, ustekinumab, secukinumab, and infliximab have also been used successfully [39, 40, 45, 46]. Further development of IL-36 targeted inhibition strategies is needed to better manage DITRA patients particularly in pediatric population.

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16 Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne (PAPA) Syndrome

Antonella Insalaco

Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome is a rare autosomal dominant autoinflammatory syndrome first described by Lindor et al. in 1997 [1], characterized by early onset of recurrent episodes of severe inflammation of skin and joints.

16.1 Clinical Features

PAPA syndrome presents typically with recurrent episodes of sterile, pyogenic, pauciarticular, and peripheral arthritis in early childhood, occurring spontaneously or after minor trauma (Fig. 16.1). Recurring inflammatory episodes lead to accumulation of sterile, pyogenic, neutrophil-rich material within the affected joints occasionally resulting in significant joint destruction [2]. Radiographic findings include periosteal proliferation of involved bones and, in some cases, ankylosis [1, 2]. Skin involvement is more variable and may predominate as patients progress to puberty. It is also episodic and recurrent and can include aggressive ulcerative skin lesions, often of the lower extremities, indistinguishable from pyoderma gangrenosum (Fig. 16.2) or severe cystic acne, which begins in adolescence and persists into adulthood [1–3] (Fig. 16.3). Although the synovial fluid and skin lesions may have the appearance of an infectious process, culture of skin and joints is sterile. Other possible manifestations of the PAPA syndrome include pathergy (the formation of sterile abscesses at injection sites), sporadic episodes of irritable bowel syndrome, aphthous stomatitis, and, reported in one family, pancytopenia after administration of sulfa-containing medications [1, 2].

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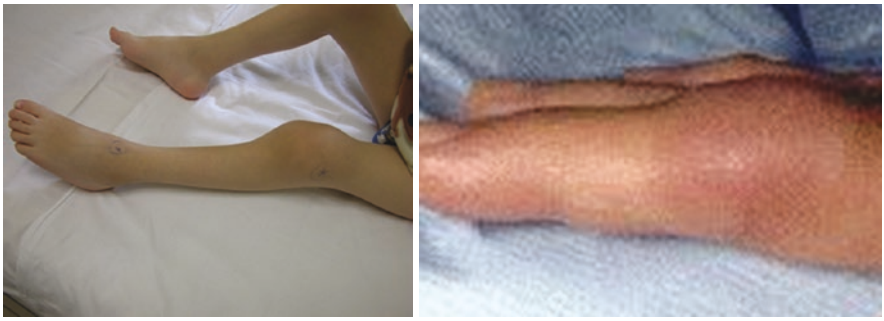

Fig. 16.1 Peripheral joint involvement in patients with PAPA syndrome. *Source*: Courtesy of Dr Marco Gattorno

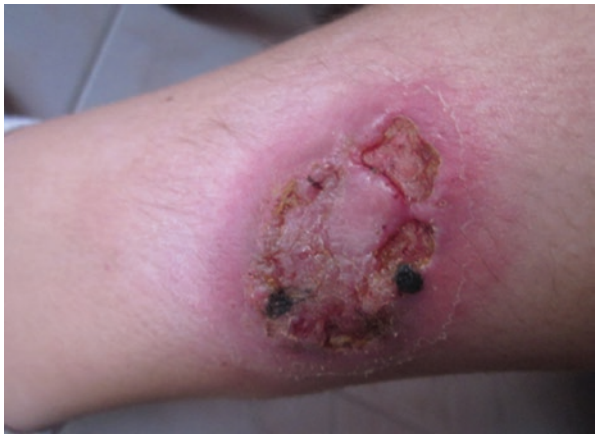

Fig. 16.2 Pyoderma gangrenosum in a patient with PAPA syndrome

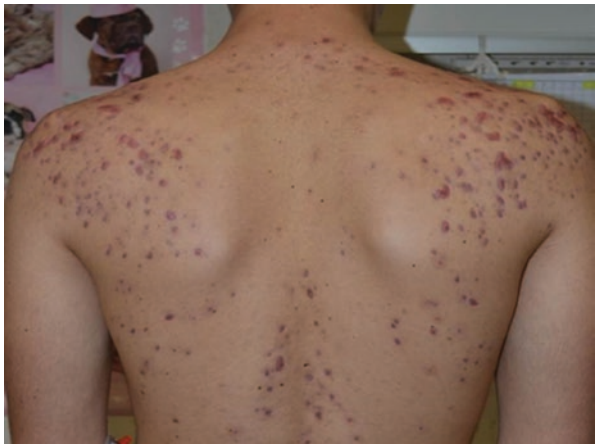

Fig. 16.3 Cystic acne in PAPA syndrome begins in adolescence and persists into adulthood

16.2 Pathogenesis

PAPA is caused by different mutations in the proline-serine-threonine phosphatase-interacting protein (PSTPIP1) gene, located on chromosome 15 [4]. PSTPIP1 is a cytoskeleton-associated adaptor protein that was originally identified in the mouse through interaction with PEST (rich in proline (P), glutamic acid (E), serine (S), and threonine (T) residues-type protein tyrosine phosphatase (PTP-PEST, also known as PTNP12) [5]). The human homolog, called CD2-binding protein1 (CD2BP1), was identified by interaction with the T cell surface protein CD2 [6]. PSTPIP1/CD2BP1 protein links PEST-type phosphatases to their substrates [7]. The binding of PTP-PEST to PSTPIP1 is essential for its dephosphorylation. Mutations of PSTPIP1 severely abrogate binding to PTP-PEST causing the hyperphosphorylation of PSTPIP1 itself [3, 8]. PSTPIP1 protein also interacts with Wiskott–Aldrich syndrome protein (WASP) and with the pyrin inflammasome. Disease-causing *PSTPIP1* mutations diminish the interactions with PEST-type proteins or WASP and increase interaction with pyrin [9]. The PSTPIP1/CD2BP1 protein acts as a scaffold protein participating in the organization of the actin cytoskeleton [10] and modulates T cell activation [11] and IL-1β release. The last mechanism is due to interaction between PSTPIP1 and Pyrin, the familial Mediterranean fever (FMF) protein that, in association with the cytoskeleton, in myeloid/monocytic cells, modulates IL1β processing, NF-kb activation, and apoptosis [9]. The originally identified PSTPIP1/CD2BP1 causing mutations, A230T, and E250Q, as well as others subsequently described, increase the strength of the interaction between PSTPIP1 and pyrin interfering with the ability of PSTPIP1 to phosphorylate proinflammatory pyrin domain, eventually leading to an altered assembly and activation of the inflammasome and consequent release of IL-1β. Increased avidity of PSTPIP1 for pyrin leads indeed to the formation of macromolecular complexes, so-called "pyroptosomes" that recruit and activate caspase-1, an inflammasome component, leading to cell death and to the release of inflammatory cytokines such as IL-1β [3, 4, 9, 12]. While disease-causing mutations in PSTPIP1 affect pyrin-mediated pathways, the reverse does not happen; indeed FMF causal mutations do not affect binding to PSTPIP1 [3]. The overexpression of IL1-β induces an uncontrolled production of several proinflammatory cytokines and chemokines, which are responsible for the recruitment and activation of mature neutrophils, leading to a neutrophil-mediated inflammatory scenario [10, 13]. Furthermore, PAPA syndrome macrophages exhibit a specific defect in the directed migration and a significant defect in podosome formation with many cells forming few altered podosomes. Defects in mononuclear cell podosome formation and migration have been reported in patients with WASP mutations and the primary immunodeficiency disorder Wiskott–Aldrich Syndrome (WAS). The similarities in macrophage morphology from patients with both PAPA syndrome and WAS suggest that PSTPIP1 may regulate macrophage podosome formation through its interaction with WASP. During the inflammatory phase, macrophages must navigate the granulation tissue to clear apoptotic neutrophils. Abnormal macrophage trafficking and retention of macrophages within tissues because of

impaired migration may contribute to the development of chronic inflammation through neutrophil recruitment [14]. A hallmark of PAPA syndrome is the very high expression of two pro-inflammatory proteins of the S100-family, MRP8 (S100A8) and MRP14 (S100A9). These proteins belong to the family of so-called "alarmins" or danger-associated molecular pattern (DAMPs), which are released during cell stress or damage at the local site of inflammation [15]. The exact role of these molecules in the pathogenesis of PAPA is yet not clear. Extracellular MRP8 and MRP14 form a positive inflammatory feedback loop with IL1-β, playing a significant role in the autoinflammatory process of PAPA syndrome.

To date, several missense mutations have been described in an online database of mutations (http://fmf.igh.cnrs.fr/infevers/). Mutations in PSTPIP1 are incompletely penetrant and variably expressed in the PAPA syndrome [16]. Interestingly, some cases of PAPA syndrome have proven negative for PSTPIP1 mutations [17].

16.3 Other PSTPIP1-Associated Inflammatory Diseases

In the last years, the spectrum of autoinflammatory diseases due to mutation in PSTPIP1 with distinct clinical phenotypes has been expanded, indicating that PAPA syndrome is only one clinical entity within the spectrum of PSTPIP1-associated inflammatory disease, so-called "PAID" [16]. Other related syndromes have indeed recently been described: PASH (pyoderma gangrenosum, acne, and suppurative hidradenitis) syndrome [18], PAPASH (pyogenic arthritis, pyoderma gangrenosum, acne, and suppurative hidradenitis) syndrome [19], PAMI (PSTPIP1-associated myeloid-related proteinemia inflammatory), and PAC (pyoderma gangrenosum, acne, and ulcerative colitis) syndrome [20, 21] (Table 16.1). PASH syndrome has been described in 2011 in two unrelated patients as an autoinflammatory disease of the skin, clinically characterized by pyoderma gangrenosum, acne, and suppurative hidradenitis. No recurrent arthritis was observed in these patients. No coding mutations in PSTPIP1 were identified, but an increased repetition of the CCTG microsatellite motif was present in the PSTPIP1 promoter on one allele in both patients [18]. Some years later, a new entity, characterized by pyogenic arthritis, pyoderma gangrenosum, acne, and suppurative hidradenitis, called PAPASH, was described in one patient [19]. The p.E277D missense mutation of the PSTPIP1 gene was found in that case. In 2016, PSTPIP1-associated myeloid-related proteinemia inflammatory (PAMI) syndrome has been defined as another distinct autoinflammatory

Table 16.1 PSTPIP1-associated inflammatory diseases (PAID)

Acronym	Syndrome
PAPA	Pyogenic arthritis, pyoderma gangrenosum and acne
PASH	Pyoderma gangrenosum, acne, and suppurative hidradenitis
PAPASH	Pyogenic arthritis, pyoderma gangrenosum, acne, and suppurative hidradenitis
PAMI	PSTPIP1-associated myeloid-related-proteinemia inflammatory syndrome
PAC	Pyoderma gangrenosum, acne, and ulcerative colitis syndrome

disorder presenting clinical and biochemical features not found in patients with classic PAPA syndrome [20]. In addition to skin inflammation and arthritis, PAMI is characterized by chronic systemic inflammation, hepatosplenomegaly, and pancytopenia. Bone marrow involvement, hyperzincemia, and extremely high levels of pro-inflammatory alarmins myeloid-related protein (MRP) 8/14 distinguish PAMI from PAPA. It is due to p.E250K and p.E257K mutations that result in charge reversal in the y-domain of PSTPIP1 (E→K) and increase interaction with pyrin [20]. Finally, PAC syndrome, consisting of pyoderma gangrenosum, acne, and ulcerative colitis, has also been described [22].

16.4 Treatment

Because of its rarity, clinical heterogeneity, and the complex pathogenesis, patients with PAID still lack a well-defined therapeutic approach. In addition to steroids, in line with the presumed common pathogenesis involving IL-1-driven inflammation, collective experience so far indicates that IL-1- and TNF-targeted therapies represent the most successful treatment solution in order to obtain prolonged remission.

Arthritis responds to corticosteroid therapy; however, the associated adverse effects often limit steroid use. Consistent with the pathogenesis, leukocytes from patients produce increased levels of IL-1β in vitro [9], which is a potent inducer of TNFα [23], raising the possibility that treatment with biological agents may be helpful. There are reports of successful treatment with etanercept [23], infliximab [24], anakinra [16, 25–27], and canakinumab [28] in some patients. There is anecdotal evidence that IL-1 inhibition may be more beneficial for joint manifestations and TNF inhibition for pyoderma gangrenosum. However, there is no consistently successful treatment for this syndrome. Significant variability in response has been observed; biologics have not been consistently effective and do not necessarily induce remission of all the disease manifestations, raising interesting questions about the pathogenesis of each feature of the diseases. Since PSTPIP1 may potentially network with several proteins involved in the immune response, other than pyrin, it is conceivable that mechanisms different from IL-1 signaling activation may play an additional role in the pathogenesis of the disease, thus explaining the clinical peculiarity of PAPA compared with other IL-1-mediated diseases.

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